GENERATION OF LANGUAGE IN NORMAL MALES:
A REGIONAL CEREBRAL BLOOD FLOW STUDY

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Abstract of the Dissertation Presented to the Graduate School of the
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THE GENERATION OF LANGUAGE IN NORMAL MALES:
A REGIONAL CEREBRAL BLOOD FLOW STUDY

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This investigation examined regional cerebral blood flow during the generation of language.
Twelve neurologically normal right-handed males participated in this study. Subjects performed
three cognitive activation tasks, after which distribution of regional cerebral blood flow was
determined via single photon emission computerized tomography (SPECT). The three tasks were
designed to preferentially stress the phonological, semantic, and grammatical components of
language in a stepwise, hierarchical fashion. Image analysis was performed using a neuroanatomical
atlas and a magnetic resonance scan of each subject's brain in conjunction with the data given by the
SPECT scans.

Intertask analyses suggest an important role for the left posterior superior temporal region
(i.e., Wernicke's area) in tasks stressing the generation of lexical-semantic information. In addition,
intratask analyses suggest that while there are no differences in whole-brain counts across tasks, each
task does engender a distinct pattern of asymmetries between area homologues. In particular, the
findings support the role of Wernicke's area in lexical-semantic processing and provide further
support for the previously reported findings of consistent left frontal opercular involvement in
generative language and left Brodmann's area 37 in tasks requiring visual analysis of word forms. In
addition, results are consistent with the view that practice of a given activation task may change the
magnitude and pattern of rCBF observed during the subsequent performance of that task. The results
are discussed in light of current findings in the functional neuroimaging and lesion literature, and

directions for future research are discussed. This investigation reinforces the merits of studying the neural instantiation of language in the human brain with functional neuroimaging.

CHAPTER I

INTRODUCTION

The study of language has a rich history, from the seminal clinico-anatomical correlation of Paul Broca in 1861 to the functional neuroimaging studies of today (Wise, Hadar, Howard, & Patterson, 1991). The most fruitful of these efforts have been built upon careful consideration of the observed language phenomena and systematic investigation of the "building blocks" upon which these phenomena are based. For almost one hundred years, these efforts were limited to observations of patients with brain pathology that could not be quantified until autopsy. Despite these limitations, theorists such as Wernicke and Lichteim were able to generate a general framework for the instantiation of language in the brain which has held up well to the test of time (Lichteim, 1885; Wernicke, 1874). Evolving technologies and the rediscovery and elaboration of these theories by Geschwind in the late 1960's ushered in a new age of language investigation (Geschwind, 1972). The rich complexity of both the neuroanatomical and psycholinguistic components of language has sparked the interest of a variety of disciplines, and the increasing inter-reliance of cognitive, psycholinguistic, neuroanatomical, and neurophysiological investigations upon each other has the potential to provide a more comprehensive understanding of language than has been available to previous generations. Investigations built upon the theoretical foundations laid down by previous generations which exploit the capabilities provided by technological advances will be an important component to the further investigation of the "building blocks" of language in a normal population. The focus of the current study is an examination of specific components of language comprehension and generation utilizing functional neuroimaging.

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<u>Definition of Terms</u>

A careful examination of language requires an explicit definition of the phenomena to be investigated. For the purposes of this study, language will be broken down into three components: phonology, lexical-semantics, and grammar. For the purposes of this study, phonological processes will be defined as those that deal with the sequencing of individual phonemes into morphemes, which are then used to form words. Other phonological processes (e.g. linguistic prosody, accent) are not explicitly addressed in this study. Lexical-semantic processes are those that deal with meaningful concepts and the symbolic representation of those concepts (i.e. words). Specifically, lexical processes deal with words, while semantic processes deal with conceptual knowledge. While these processes have been shown to dissociate (Hillis & Caramazza, 1991), the current study makes no attempt to investigate this dissociation. Grammatical processes deal with the word- and sentence-level aspects of language which are used to conceptually elaborate upon single words and to denote relationships between words, respectively. At the single word level, changes in the inflectional and/or derivational morphology of the word are used to specify its properties. In contrast, the sentential-level properties denote the relationships between words; these properties may be referred to as the syntactic properties of a sentence. Although the terms grammar and syntax have been used interchangeably in the literature, Nadeau (1988) points out that syntactic and morphological processes are distinct both conceptually and anatomically. Further investigation of the dissociability of these components is beyond the scope of this study, and the term grammar will be used to incorporate both syntactic and morphological processes.

Functional neuroimaging studies have varied a great deal in the extent to which they have investigated these components of language. In general, the contributions of the three components to the experimental tasks which have been used to investigate language in normals have been hopelessly confounded with each other. While these investigations have been successful in showing that most language tasks do engender different patterns of regional physiological activity (blood flow or glucose metabolism) than those that are seen at rest, they have done relatively little to disambiguate the ways in which disparate psycholinguistic processes are instantiated in the brain. Perhaps the most consistent

finding to date is that measurable changes in regional measures of activity will occur during tasks that require subjects to generate language (Friston et al., 1991a; Frith et al., 1991; Ingvar & Schwartz, 1974; Petersen et al., 1988; Warkentin et al., 1991; Wise et al., 1991). Given these techniques' consistent sensitivity to gross changes involved in these tasks, the experimental manipulation of generative language tasks may be a powerful method of exploring the instantiation of different language components in the brain.

"Generation of language" is a broad construct which may be broken down conceptually. The amount of "generative capacity" demanded for a given language task may be seen to lie on a conceptual continuum. The defining characteristic of this continuum is the degree to which novel formulations of language must be produced. On one end of the continuum are tasks in which the material to be generated is largely predefined. A prime example of this sort of task is repetition. While repetition undoubtedly accesses phonological, lexical-semantic, and grammatical processes, only phonological processes (parsing of auditory stimuli into individual morphemes, sequencing these same morphemes for output, motor programming of output) need be intact to successfully perform the task across the entire range of linguistic stimuli. In addition to the predefinition of generated material by external sources, material may be predefined internally as well. An example of this sort of generative task is the production of "automatic language." Language is considered automatic to the extent to which it can be produced without cognitive effort on the part of the speaker. Examples include counting, reciting the alphabet, or reciting the months of the year. In each of these examples, the material to be generated is overlearned and exquisitely predefined.

Tasks which require novel formulations of language vary in their demands as well. A task frequently used to assess one's ability to produce language is alternately termed "verbal fluency," "controlled oral word association," or the Thurstone task (Thurstone & Thurstone, 1943). In variants of this task, output is strongly mediated by lexical or semantic constraints set up by the examiner, but the subject is responsible for the generation of single words which fit into these constraints. External mediation of language generation may be decreased by asking patients to describe pictures or generate stories around a particular theme, in which case the subject must utilize phonological, lexical-semantic,

and grammatical processes to successfully complete the task. Finally, the least externally-mediated language generation is the subject's own spontaneous speech, which the subject is solely responsible for conceptual, lexical-semantic, grammatical, and phonological formulation.

While spontaneous language generation is perhaps the best measure of the subject's overall language competence, its inherent variability between subjects and within subjects across situations makes it the most difficult to study in the laboratory. Especially during the use of functional neuroimaging, when differences in quantity of input or output may confound results meant to examine qualitative aspects of comprehension or production, the highest degree of experimental control possible while maintaining the integrity of the phenomenon under study is extremely desirable. Thus, the focus of this language investigation will be the strongly-mediated generation of novel responses in hierarchically structured phonological, lexical-semantic, and grammatical tasks in a normal population.

As visually-displayed words will be used as the mediating stimuli in this study, the following review will focus on functional neuroimaging investigations of the instantiation of single-word reading and strongly-mediated language generation in the normal brain. Consideration will be given to the ways in which these abilities have been investigated and the ways that these findings may be interpreted in the light of findings from classical aphasiology. The goal of this review is to integrate the data provided by these investigations into a coherent set of hypotheses which may be systematically examined in the context of a functional neuroimaging study.

<u>Methodological Considerations</u>

An important step in interpreting the available data is understanding the ways in which the data have been collected. While the assumptions made in interpretation of data from aphasic populations have been described extensively (Kertesz, 1983), the assumptions inherent in functional neuroimaging studies have received relatively little attention in the sources typically read by behavioral scientists. As this review makes substantial mention of both of these bodies of literature, the assumptions and limitations inherent to each will be discussed; however, given the imbalance of

attention that each has received in the literature to date, relatively more attention will be given to assumptions important to the design and interpretation of functional neuroimaging results.

<u>Aphasia/Brain Lesion Studies</u>

Clinico-anatomical correlation is the most time-honored method of brain-behavior investigation, dating back to Broca's seminal effort in 1861. This approach assumes that the importance of a given region of brain tissue to a given behavior is manifested in the degree to which that behavior is disrupted when the region is damaged. The majority of progress in understanding brain-behavior relationships has been built upon theories and investigations based upon this principle. These patients have long provided the most natural "laboratory" to investigate hypotheses built upon earlier work, and a great deal of effort has been expended to define parameters which mediate the validity of these observations (such as recovery curves, stability of lesions, etc.).

Nevertheless, this approach has limitations. First, the definition of "damage" has varied considerably from study to study and has included such disparate processes as infarction, laceration, necrosis secondary to radiation, excision secondary to neoplastic process, and electrophysiological disruption (either due to a seizure focus or due to electrical stimulation). The differences between these types of lesions in terms of etiology and effects on neighboring structures may well lead to different behavioral observations when examining the effects of a given cerebral lesion. While this limitation needs to be kept in mind when evaluating data, it may be mitigated to a large degree by careful selection of the data upon which conclusions are based. A related limitation is the uncertainty of lesion extent. The best neuroimaging technologies available today are not 100% accurate in identifying sites of cerebral pathology, and recent functional neuroimaging studies suggest that structural imaging may significantly underestimate the extent of "functional pathology" as defined by a decrease in regional glucose metabolism (Metter et al., 1986). The most severe limitation in interpretation of data from these studies, however, applies to even those studies with extensive definition of lesion location and size: the uncertainty as to whether one is observing the functioning of a damaged functional system or an alternate compensatory system. In the absence of subsequent

lesions which serve to disambiguate these issues (Heilman, Rothi, Campanella, & Wolfson, 1979), this question is unanswerable in the context of a single lesion study.

Functional Neuroimaging Studies

Functional neuroimaging studies, on the other hand, have the potential to disambiguate these issues to a greater degree due to their depiction of which areas of the brain are most physiologically active (or undergo the most change in activity) during a given cognitive task. This potential has combined with the ever-improving resolution of functional neuroimaging techniques such as positron emission tomography (PET), single photon emission tomography (SPECT), and nuclear magnetic resonance spectroscopy (NMR spectroscopy) to spur increasingly widespread use of these techniques in the investigation of brain-behavior relationships. As a result of this rapidly growing interest, however, behavioral scientists have been increasingly thrust into the role of assimilating and evaluating data which they have very little formal training in interpreting. While a great deal of excitement has accompanied the use of these "windows into the living brain," there are a number of fundamental assumptions made by many researchers and consumers alike that vary widely in terms of the extent to which they have been supported by empirical data. These assumptions are made at the levels of (1) global assumptions across techniques of functional neuroimaging, and (2) the technique-specific assumptions of image acquisition and data analysis. As a full understanding of these assumptions is necessary to the informed evaluation of these studies, they will be examined in some detail.

Global Assumptions

1. Local metabolism is indicative of local neuronal activity. The most fundamental assumption common to all functional neuroimaging studies is that the data being collected are a valid indication of neural activity. Given the critical importance of this assumption to the interpretation of functional neuroimaging studies, it has received a great deal of attention. As a result, this assumption has received the most empirical support of all of the global assumptions. If "neuronal activity" may be defined as neuronal energy production, then one of the most widely accepted indices of neuronal

activity is oxygen consumption. The vast majority of the metabolic demands of the brain are met by oxidative metabolism of glucose. Although there are rare instances in which oxygen utilization may be an inaccurate indicator of ATP production (Frackowiak & Lammertsma, 1985), these conditions are uncommon enough that O_2 metabolism is considered a reliable index of neuronal activity. Importantly, regional cerebral metabolic rate for glucose (rCMR) and regional cerebral blood flow (rCBF) have been shown to be very highly correlated to oxidative metabolism measures given by autoradiographic techniques (Kurschinsky, 1987). These relationships hold particularly strongly under normal conditions (Raichle, Grubb, Gado, Eichling, & Ter-Pogossian, 1976). However, the relationships between these variables become less consistent under certain clinical conditions (Frackowiak & Lammertsma, 1985; Harper, 1989), and some evidence suggests that they may dissociate in normals under conditions of abnormally high stimulation, although this remains a matter of some debate (Chadwick & Whelan, 1991; Collins, 1991; Fox & Raichle, 1986). When rCBF and rCMR do dissociate, rCMR seems to be the more predictable of the two indices (Chadwick & Whelan, 1991).

2. The changes seen in functional images of the brain represent changes in neuronal activity.

Recent efforts have examined the way in which the phenomena being viewed in functional neuroimaging scans are related to neuronal activity at the microscopic level (Collins, 1991). The results of these efforts have thrown an interesting wrinkle into the traditional interpretation of functional neuroimaging scans, particularly in studies of normal subjects. Since the inception of functional neuroimaging techniques in the 1960's, the majority of investigators have described significant regions of change in their data as signaling the populations of neurons that are most active (in terms of increasing or decreasing activity) in a given comparison. In fact, it has now been relatively firmly established that the changes seen in these images occur almost exclusively at the synaptic level, not at the granular level. Thus, *it is not change in activity in cell bodies that is reflected in these scans, but rather change in the level of synaptic activity in a region* (Chadwick & Whelan, 1991; Collins, 1991). This dynamic has been supported in a number of investigations. Examples include

autoradiographic investigations of the effects of eye-patching on glucose utilization in striate cortex in rhesus monkeys (Kennedy et al., 1976), the effects of salt-loaded diets on hypothalamic-hypophysial glucose utilization in rats (Schwartz et al., 1979), and the effects of sciatic nerve stimulation on glucose utilization in the dorsal root ganglia and lumbar spinal cord in anesthetized rats (Kadekaro et al., 1985). This later study showed a quantitative relationship between the frequency of stimulation and the rate of glucose utilization in the dorsal horn of the lumbar spinal cord, while no significant changes in glucose metabolism occurred in the dorsal root ganglia.

Such a dynamic is also supported by recent findings in the microarchitecture of the brain (Collins, 1991). Regions of high metabolic activity in the brain are marked by increased concentrations of the mitochondrial enzyme cytochrome oxidase (Wong-Riley, 1989). Correspondingly, there is a clear relationship between cytochrome oxidase and capillary density in laminated structures in the rat brain, and capillary density has shown to vary closely with variations in the magnitude of brain glucose utilization (Borowski & Collins, 1989a). The relationship between cytochrome oxidase and capillary density appears to be stronger in the neuropil than in cell bodies. Regions that show the highest degree of cytochrome oxidase activity are typically dendrite tips with spines and glomeruli (Collins, 1991). Conversely, proximal dendritic shafts show lower concentrations of cytochrome oxidase and higher concentrations of glycolytic enzymes, such as lactate dehydrogenase. There is an inverse relationship between capillary density and lactate dehydrogenase activity (Borowski & Collins, 1989a).

These findings have profound implications for interpretation of functional neuroimaging studies. For instance, use of the term "activation" in describing the neuronal events occurring during stimulation may well be a misnomer. If one is examining a region in which the majority of the activity in the dendritic fields is inhibitory in nature, then an "increase in activity" may in fact signal a *decrease* in the activity level of the cell bodies in the region. Thus, the only way to determine the actual change in activity level of the region is to look "downstream" at the region's efferent sites and see if they are affected as would be expected given an increase in the region's activity. Given the multiplicity of afferents to most regions in the brain, this is extremely difficult to do using in vivo studies in which

areas within human brains are activated through behavioral methods. Studies using animal models (e.g., Mitchell, Jackson, Sambrook, & Crossman, 1989) have shown greater success in tracing "downstream activity," although such studies are not without problems.

An important related issue which has yet to be sufficiently addressed in the literature is the relative contributions of intra– and inter–regional inputs into a given region. If the data are correct in suggesting that functional images are indicative of synaptic rather than cell body activity, then the relative contributions of these sources play a critical role in the interpretation of "activation." If, indeed, the majority of the synaptic activity in a region of interest is the result of local interneuronal activity, then the traditional interpretation of functional images may be closer to the truth than would be the case in a region whose synaptic activity was primarily the result of afferent pathways from other regions in the brain. Intuitively, it is likely that the ratios of these inputs vary across different regions of the brain, and it is conceivable that the ratios may even vary within regions according to the demands placed upon a given region at a given time.

3. The degree of activity in a region is indicative of the importance of that region to the phenomena being studied. This assumption appears to stem indirectly from the clinico-anatomical correlational approach described earlier. While the technological limitations of the times limited the data available to the original European investigators of aphasia (Broca, Wernicke, Lichteim, etc.) to post-mortem structural information, later developments enabled investigators to extend this model to more accurately-defined anatomical lesions as well as to metabolic abnormalities secondary to these lesions (Alexander, Naeser, & Palumbo, 1990; Benson, 1967; Metter et al., 1989; Mohr et al., 1978). As the reasoning in this research suggested that those regions which were hypodense or hypoperfused were regions important in the etiology of the language disturbance, it was a relatively short step to assume that those areas that "light up" in functional neuroimaging studies of the normal brain must be those that are most important to the behavior at hand.

The recent anatomical findings mentioned earlier complicate this leap in reasoning, however. In patients with brain lesions, interpretation is simplified by the identifiable lesion. Hypoperfusion in

the area of the lesion is accounted for by death of the afferent terminals and/or cessation of interneuronal activity, while remote hypometabolic effects are explained by a lack of activity in the damaged region's efferent terminals as well as silent ischemia and neuronal dropout (Metter et al., 1986; Nadeau & Crosson, 1992). In normals, one is seeing analogous input and output functions, but there is no area of cell death to easily demarcate the activity level of a given region. Thus, in functional neuroimaging studies, one is limited to a modification of assumption #3, which might be stated as "The degree of *change in synaptic activity in a given region* is indicative of the importance of that region to the phenomena being studied." While the original assumption of neuronal activity in a region being important to the behavior being studied is certainly not discarded, it is much more difficult to investigate given that these techniques do not show change in activity at the level of the cell bodies.

   4. The scale by which activity is quantified in functional neuroimaging studies is proportional to a physiologically "meaningful" scale in some sense, and this scale has the same meaning across all regions of the brain. This assumption is made by those investigators who compare changes in activity levels across regions or who use global change as an index to which regional changes are referenced. Thus, if one observes a 30% increase in rCBF in the right dorsolateral frontal lobe and a 15% increase in the left dorsolateral frontal lobe, then one assumes that the right dorsolateral frontal lobe is "more important" to the phenomena at hand. Furthermore, it is presumed that the 15% increase in activity in one region is functionally equivalent to a 15% increase in the another region (in terms of the size and increments of the scale on which rCBF is measured). Thus, a consistent "potential change in blood flow" range is posited over the entire brain. Given the wide variability in arterial supply across regions of the brain as well as the varying neuron densities across regions, this may well be a tenuous assumption. Given the strong relationship between capillary density and regional glucose metabolism (Borowski & Collins, 1989a), it may be that regions with greater capillary density have a greater range of potential metabolic values. If this is the case, then percentage increases in regional metabolism/blood flow may have dramatically different implications across different regions, as the

differences in potential range of values serve to put the different regions on different scales of measurement.

A concrete example might help to illustrate the point. Investigations comparing the reactivity of different areas of cortex suggest that behavioral activation may induce changes in primary motor and sensory cortices of up to 40%; in contrast, the changes induced in association cortices may be as low as 2 to 5% (Raichle, 1987). This potential confound must be kept in mind for any algorithm that references change to other regions. Indeed, depending upon the size of the investigator's regions of interest, this confound may have a substantial impact upon data from *within* regions. As different areas of cortex may have different scales of potential activity levels (and gray and white matter are certainly different), one must temper conclusions about changes in activity with the knowledge of exactly which regions are being measured.

5. The activity measured is relatively consistent across the time of measurement. The issue of temporal resolution is one that is receiving increasing attention in the literature (Chadwick & Whelan, 1991). Despite years of electrophysiological data detailing the change in neural areas in increasingly short intervals, few functional neuroimaging studies discuss this issue. In fact, the time taken to acquire data varies tremendously between techniques, with a current low of approximately 40 seconds for PET using ^{15}O-labeled water to approximately 40 minutes for PET using ^{18}F-2-fluoro-2-deoxy-D-glucose. The methods that have been used to investigate language in normals acquire the majority of their data within six minutes of tracer administration. To date, no group has systematically evaluated the impact that differences in data acquisition time have upon the pattern of regional activity that is observed, although some work has been done showing that relatively small differences in stimuli presentation rate can engender different patterns of activation during performance of the same cognitive task (Raichle, 1991).

Technique-Specific Issues

In addition to the assumptions made across functional neuroimaging techniques, each technique must come to grips with a common set of issues. These issues involve (1) the manner in which data are acquired, (2) the construction of the images that are meant to reflect, and (3) the correspondence of these images to the physiological phenomena they are meant to reflect (both in terms of numbers to actual metabolism/blood flow and in terms of localizing a given structure). Finally, the nature of the experimental tasks themselves is crucial to any interpretation of data. An exhaustive review of the techniques that have been used to deal with these issues is beyond the scope of this paper. Instead, attention will be paid primarily to those methodologies used in the work most applicable to the study of single-word reading and language generation in normals.

Single Photon Emission Tomography (SPET) The earliest functional neuroimaging studies of language generation in normals (Ingvar & Schwartz, 1974; Larsen, Skinhøj, & Lassen, 1978) were done using single photon emission tomography (SPET). In the early versions of this technique, the radiopharmaceutical is administered via intracarotid injection and blood samples are taken from the jugular vein to provide indices which are later used in data correction. Localization is performed by superimposing markers placed in certain detector fields onto markers placed in the same location and then scanned by X-ray or CT.

Obviously, the method of data acquisition employed by this technique has major limitations. It is extremely invasive, such that only subjects undergoing carotid angiography for suspected arterial aneurysm or A-V malformation are eligible for participation (Lassen, 1985). This casts immediate doubts on the "normality" of the population when exploring the neural instantiation of "normal" cognitive function. In addition, the subjects are in an extremely unusual setting, with collimators placed directly over their heads and needles in their necks, and the impact that these far-from-normal circumstances has upon "normal" cognitive activity is not clear. The construction of the images is a relatively straightforward matter, but the early investigations were limited to studying one hemisphere at a time. This obviously limits the questions that may be asked of the data. The extent to which the

counts are reflective of neural activity in a given region is also difficult to interpret in this methodology, due to the manner in which the data are acquired. Since the detectors are placed over fixed locations for a given period of time, they are integrating all activity in their "field of view" over that period of time. Given the orientation of the detectors, this means that cortical, subcortical, and possibly even contralateral areas may be contributing to the activity index at any given detector (Risberg, 1980).

Later SPET research (Risberg, 1980; Warkentin et al., 1991) utilizes ^{133}Xe inhalation rather than intracarotid radiopharmaceutical injection. In addition, this technique allows simultaneous scanning of both hemispheres. The primary advantage of this technique over its predecessor is its noninvasiveness. In addition, given the nature of the radiation emitted by ^{133}Xe, a number of repeat scans may be performed on the same subject at 30 minute intervals without danger of excessive radiation exposure. Another advantage of the later SPET research is the use of numerical algorithms to reduce the contribution of counts from regions other than the cortex of interest to the acquired data (Risberg, 1980). A related limitation of this technique is the steps required in the analysis of the data. Due to radiation scatter (primarily due to airway artifacts), the data that "count" towards the indices of activity are not collected until 1.5 to 2 minutes after the administration of the ^{133}Xe, and data collection is then continued for five to ten minutes afterwards (depending upon the specific technique). These aspects of the temporal resolution of the technique must be kept in mind when interpreting results.

Single Photon Emission Computerized Tomography (SPECT)   SPECT utilizes some of the same principles pioneered in the SPET research and applies them to three dimensional computerized tomography. The method of data acquisition in this technique depends upon the tracer that is used. In those studies using ^{133}Xe-inhalation, the data acquisition is virtually identical to the ^{133}Xe-inhalation SPET studies. The primary advantage of this technique over the SPET studies is the improved image resolution and the capability to examine the data in three dimensions. In addition, newer tracers used

with SPECT have compared very favorably to PET in terms of image resolution and replicability (Gemmell et al., 1990; Inugami et al., 1988).

Positron Emission Tomography (PET). The results which have received the most attention in the functional neuroimaging of normal brain function are those produced by laboratories utilizing PET. In PET, data are acquired by means of detectors which encircle the head of a subject who has received an injection of radiopharmaceutical. The length of time which elapses between administration of the tracer and data acquisition varies according to the tracer. The tracers most commonly administered in investigations of normal language are IV injections of ^{15}O-labeled water and inhalation of $C^{15}O_2$. ^{15}O has a very short half-life (2.05 minutes), and may thus be used for a number of repeat scans of the same subject with relatively little radiation exposure. In addition, a complete scan may be taken as quickly as 40 seconds following administration of the tracer. This short interval is not without costs in terms of image sensitivity, however (Iida et al., 1991). Due to the radioactive properties of the tracers used in PET, spatial resolution is improved relative to SPECT. The construction of the images to be analyzed varies from lab to lab (Fox et al., 1988; Friston et al., 1990), and these will be discussed later in context of the studies that use them.

Many aspects of the data acquisition in PET are superior to those of other methodologies (Raichle, 1983). The nature of the radionuclides (particularly ^{15}O, ^{13}N, and ^{11}C) are such that they decay with a relatively high degree of energy, thus enhancing their detectability and the resolution with which images may be reconstructed. As previously mentioned, their short half-life may be advantageous in some situations. They are also readily incorporated into substances that will be included in most metabolic processes, thus increasing their flexibility. The disadvantages of PET are primarily procedural in nature. Due to the nature of ^{15}O and the current models of analysis, one is limited to no more than 40 seconds of an experimental manipulation before analysis of regional cerebral blood flow, on peril of severely underestimating true rCBF (Iida et al., 1991; Raichle, 1985). While this fact has the advantages enumerated above, it also limits the phenomena one is capable of studying. The highly mathematical transformation of raw count data to the three dimensional

tomographic image is also not without error, although it is assumed that the error due to estimation of rCBF using ^{15}O is less than 10% (Herscovitch, Markham, & Raichle, 1983; Jones, Greenberg, & Reivich, 1982).

In terms of localization of activity, the three most frequently cited methodologies (those of Raichle and colleagues at Washington University in St. Louis, Friston, Frackowiak, and colleagues at Hammersmith Hospital in London, and Evans and colleagues at Montreal Neurological Institute) share the common feature of image standardization. These laboratories convert each subject's PET data to a standardized three-dimensional Cartesian format (that of Talairach and Tournoux, 1988). Although each lab accomplishes this in slightly different ways (Fox, Perlmutter, & Raichle, 1985; Friston et al., 1989), the end result is that each subject's brain is altered so as to fit the standard Cartesian coordinate space to enable comparisons between subjects. While this is an admirable goal in terms of maximizing statistical power and generalizability of results, it has some conceptual problems. As Steinmetz & Seitz (1991) point out, the structural variability between individual brains is so great as to severely compromise the interpretation of scans that have been "averaged" across subjects. Likewise, recent work by Black et al. (1990) and Dietrich et al. (1982), as cited by Collins (1991), has suggested that the synaptic, enzymatic, and microvascular structure of the rat brain is subject to change based upon the animal's experience. Assuming that this dynamic may be generalized to the human brain, then the interindividual variability discussed by Steinmetz and Seitz is compounded even further. In addition, work by Phillips and his colleagues (1990) suggests that measurements of regional cerebral glucose may err by up to 20% as a result of very minor misalignments of multiple scans of a single subject. When one considers the variability already inherent in interindividual comparisons, this error rate suggests that standardization of images will underestimate areas of regional change at best and will falsely identify areas of regional activation at worst. Thus, conclusions based upon standardized scans must be tempered with a great deal of caution, especially since these groups tend to choose individual pixels (local maxima) as their regions of interest.

Another trend in the analysis of functional images is the normalization of the physiological values across scans to some index, usually either mean whole brain or hemispheric blood flow. This is

done to allow comparison of various regions while controlling for fluctuations in whole brain blood flow that may be unrelated to the task at hand, such as alterations in pCO_2 or differences in tracer uptake; thus, observed changes are not merely reflections of global phenomena affecting the whole brain. However, this technique makes a number of assumptions. First, one assumes that the changes in the regions of interest do not play a significant role in influencing the index to which the values are being normalized. In comparing cognitive activation studies, this assumption has not yet been disconfirmed. To date, significant changes in whole-brain blood flow have been seen only when comparing cognitive activation studies to either a "rest" task or a motor task.

The second assumption that such normalization makes, however, has recently come under attack. This assumption is that a change in the reference region (i.e. whole brain) will have the same proportional effect on all regions of the brain. Recent findings by Friston et al. (1990) suggest that this is not the case, but rather that areas of high flow are disproportionately increased relative to low flow areas given a fixed increase in global brain blood flow (gCBF). Such a relationship would tend to magnify the changes in high flow areas relative to low flow areas after normalization. Friston and his colleagues suggest that this difficulty may be circumvented by removing the variance in the ROI due to changes in gCBF by conducting an analysis of covariance (ANCOVA) with ROI activity as the dependent variable, gCBF as the covariate (or "nuisance variable"), and task as the categorical independent variable to determine the effects of cognitive activation on the ROI with the effects of gCBF "partialled out." The manner in which this is done will be discussed later in context of the Hammersmith studies. The issue to be emphasized here is that the assumption of proportional effects across regions of whole-brain normalization may be flawed, to the detriment of the ability to detect change in low-flow regions. In important related question which has yet to be fully addressed is the extent to which this discrepancy between high-flow and low-flow regions is attributable to differences between gray and white matter or to differences between regions of gray matter.

A vitally important issue to the interpretation of functional neuroimaging studies is the manner in which change in activation is assessed. Perhaps the most widely-cited algorithm for assessing change between images is the subtraction methodology devised primarily by the St. Louis

group (Fox, 1991). As pointed out by Raichle (1991), the subtraction paradigm is based on thinking that can first be seen in the 19th-century work of Donders, who used increments in reaction time to dissect out the components of mental operations (Donders, 1969). As applied to subtraction methodologies in functional neuroimaging, this thinking suggests that if one subtracts the pattern of brain activation seen in task A from the pattern of activation seen in task B, one discovers which populations of neurons are recruited to handle the increased demands of task B. Furthermore, if one averages the changes engendered by a given task across subjects, one can minimize the "noise" inherent in individual subtractions and obtain a more accurate picture of the common regions which are most important to the tasks.

There are a number of assumptions made by this sort of analysis which may be problematic. First, this approach assumes that the "noise" that is washed out by the combination of images does not yield valuable information in and of itself. In addition, the subtraction methodology employed by Petersen and colleagues implicitly assumes that the brain handles increasingly complex language activation by simply recruiting more neurons, while, in fact, some research suggests that the brain may handle different linguistic tasks by the activation of different systems rather than by addition of systems (Berndt, 1988; McCarthy & Warrington, 1984).

There are a number of more technical details of functional neuroimaging which have remained unaddressed by this brief review (attenuation, smoothing, and reconstruction algorithms, among others) that are not without effect on the data reported by various authors. However, for the sake of brevity, these issues will not be discussed in the current paper, and the reader is referred back to the cited sources for more information.

CHAPTER II

REVIEW OF THE LITERATURE

The topics of single word reading and strongly mediated language generation have received a great deal of attention from a number of labs employing widely different investigative techniques. Due to the plethora of data available on these topics, selected studies will be presented which are felt to reflect the current understanding of the instantiation of these functions within the brain. Particular emphasis will be placed upon interpretation of the data provided by a relatively exhaustive review of the normal-population functional neuroimaging studies in light of data provided by investigations of aphasic populations.

In order to focus the manner in which the review will be conducted, a conceptual framework is useful to define terms and illuminate specific areas of investigation. Given the array of disciplines with a vested interest in the investigation of language and the fine detail required to do careful studies of psycholinguistic phenomena, a number of conceptual frameworks have been proposed. These frameworks are most useful as heuristic devices which define the investigators' thinking rather than as guidelines by which the brain must behave in processing language. It is in this capacity that the present study will use a framework based on that proposed by Ellis and Young (1988: see Figure 2-1). It is readily acknowledged that other models have been presented to (1) describe similar phenomena, (2) break down aspects of phenomena considered relatively unitary in this model, and (3) explain language phenomena not included in this model. A discussion of these alternative models is beyond the scope of the current review, as is a complete description of the derivation of Ellis and Young's model. Rather, the model is presented and modified to provide a focus on the language phenomena to be examined in this study; namely, the phonological decoding of nonwords, the comprehension of single words and the generation of single conceptual units (nonwords, real words, or sentences). The

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two processes of interest to this study that are not explicitly addressed by this model are the drive to generate language and the grammatical formulation of output, both of which will be discussed in the review of the available data.

Alexic Deficits in Single Word Reading

Like all "omnibus" linguistic functions, reading single words is a complex act made up of a number of dissociable components. A fundamental component of reading is, of course, the visual analysis of the written word. A detailed discussion of the basic perceptual mechanisms involved in this process is beyond the scope of this review; rather, the focus will remain on psycholinguistic analysis of the visual stimulus. An extensive body of literature examining the neural instantiation of single word reading has been compiled in investigations of aphasic and alexic patients. These investigations have enabled the delineation of certain dissociations in the language system in a broad sense and within the reading system specifically.

The process by which one reads has been a topic of ongoing investigation. Specifically, the question arises as to whether all words are read in a similar manner, or if the reading process varies according to some systematic criteria. Investigations of these questions have consistently shown that reading in fact is not a unitary phenomenon, and that reading is susceptible to lexical, semantic, grammatical, and contextual effects (Ellis & Young, 1988). For the purposes of this review, only those dissociations dealing directly with lexical and semantic influences on reading performance will be discussed.

Consistent differences between reading real words and reading nonwords have been shown by a number of investigators. For instance, in normal readers, real words are read more quickly than nonwords, even when the two are equated for length and phonological complexity (Monsell, Graham, Hughes, Patterson, & Milroy, 1992). These differences become even more apparent in phonological and surface alexia. Patients with phonological alexia are able to read real words without difficulty, but they are not able to read nonwords without a disproportionate amount of effort (if at all). Conversely, patients with surface alexia are quite capable of reading nonwords, but their reading of irregular real words is impaired (Beauvois & Derouesne, 1979; Marshall & Newcombe, 1973; Rapcsak,
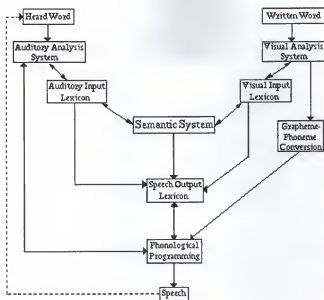
Figure 2-1. Organizational Heuristic based on Ellis & Young (1988).

Gonzalez Rothi, & Heilman, 1987). This double dissociation of reading abilities has been interpreted as suggesting the existence of two routes of reading, one relying upon lexical identification and one relying upon letter-by-letter analysis (or grapheme-to-phoneme conversion). Data suggest that normal readers rely primarily upon lexical identification in order to maximize reading efficiency (Coltheart, 1980).

Data describing the lesions responsible for these deficits are somewhat inconsistent. The angular gyrus has been identified as important to both reading and writing, as lesions to this region have been shown to produce alexia with agraphia (Benson & Geschwind, 1967; Dejerine, 1891). Alexia without agraphia, on the other hand, is typically associated with lesions to left calcarine cortex and the splenium of the corpus callosum (Damasio & Damasio, 1983). These lesions are felt to disconnect the angular gyrus from visual input, thus preventing its performing its function of processing of word images (Dejerine, 1891, 1892; Geschwind, 1965). Recent data have broken down this scheme even further. Based on the phonological alexia of a patient with a left inferior temporo-occipital lesion (Brodmann's areas 21, 37, and underlying white matter), Rapcsak, Gonzalez Rothi, & Heilman (1987) suggested that the lexical reading route may be mediated by an intact dorsal pathway from the inferior visual association cortex to Wernicke's area via the angular gyrus, while the nonlexical phonological reading route may be mediated by a ventral pathway from inferior occipital association cortex to Wernicke's area via the posterior-inferior portion of the left temporal lobe. Anderson, Damasio, and Damasio (1990) have also reported an interesting case in which a small left premotor lesion (in the area classically defined as Exner's area) appears to have severely impaired lexical reading and totally impaired nonlexical phonological reading for words but not numbers. The patient was also agraphic. The alexia, combined with the authors' report that three of four others patients with similarly located lesions were alexic acutely, suggests that this region may play some role in conjunction with the classically defined posterior cortices in the reading process. The nature of this role is uncertain, however.

Functional Neuroimaging of Single Word Reading

      To date, only two groups of investigators have reported results pertaining to basic processes involved in normal reading. The most completely reported work is that of Petersen and his colleagues (1989, 1990). The first study by this group used PET to study changes in rCBF engendered by a variety of cognitive tasks. One of the analyses that was performed compared the pattern of activity seen during the passive observation of high frequency English nouns to the pattern of activity seen during visual fixation on a crosshairs. The nouns were presented at a rate of 1 Hz. The authors report that this comparison identified striate cortex, left basal ganglia (possibly putamen), bilateral temporo-occipital cortex (junction of Brodmann's areas 37 and 19), and an area in right temporo-occipital cortex (area 37) slightly inferior to the bilateral foci as becoming significantly activated. The bilateral activation temporo-occipital activation was asymmetrical, with the left side increasing approximately 30% more than the right. In their 1990 study, this group further explored the response of the visual system to word-like stimuli. In this study, the investigators compared the patterns of activity seen during observation of (1) a blank screen (control condition), (2) false fonts, (3) consonant strings (e.g., JVJFC), (4) nonwords that followed spelling rules of English (pseudowords), and (5) regular common nouns. Three control scans were taken, and the one (or the combination) used in comparisons with stimulation tasks was not identified. In addition to the asymmetrical activation at the junction of areas 37 and 19 described in the earlier study, the investigators also noted a significant increase in left medial extrastriate cortex counts (perhaps medial area 37) during the observation of real words and pseudowords. This activation was not present in the comparison of the control scan(s) to orthographically irregular letter strings or false fonts. In addition, subtraction of the pseudoword image from the real word image suggested an area of activation in the left inferior-lateral prefrontal region (in Brodmann's area 45 or 47, anterior to Broca's area).

      The other group that has explored the response of the visual system to real words is based at the Montreal Neurological Institute. Unfortunately, none of the work with visual stimuli done by this group has been published in complete form, and references are limited to presentations and abstracts. As such, informed evaluation of these studies is impossible. The results that have been reported will

be discussed with these cautions in mind. Similar to Petersen and colleagues (1989), Marrett and coworkers (1992) contrasted the rCBF pattern seen while passively reading words to that seen when fixating on a crosshairs. They reported strong bilateral activation in striate and extrastriate cortices as well as unilateral activation in the left temporo-occipital and anterior temporal cortices (exact location unspecified). Chertkow (1990, as cited by Posner & Carr, 1992) reported similar results in the same comparison.

Obviously, there are processes other than basic visual analysis occurring when one reads single words. Both lexical and semantic processes are involved, as are processes involved in the comprehension of inflectional and derivational morphology. Although the dissociation of these components has received a great deal of attention in the cognitive neuropsychological literature (Hillis & Caramazza, 1991), the neural instantiation of these components is probably beyond the capacity of the current functional neuroimaging techniques. Thus, investigations have focused on paradigms which lump the disparate processes together and seek to differentiate their neural instantiation from that of the processes involved in the translation of visual patterns to phonological information.

The investigations examining the "higher cognitive processing" (i.e. combination of lexical, semantic, and grammatical functions) of single words explicitly require the subject to take an active role in processing the stimuli in order to examine processes beyond simple visual analysis of the stimuli. In one of these studies, Petersen and his colleagues (1989) instructed subjects to keep track of the proportion of dangerous animals that were named in the presented words. The two versions of this task set the ratios at 1/40 and 20/40. The rCBF pattern was then compared to that engendered by maintenance of visual fixation on a crosshairs that was placed above nouns. In both tasks, words were presented at a rate of 1 Hz. Subtraction of the crosshairs-observation scan from the animal-tracking scan revealed a significant rCBF increase in the anterior cingulate gyrus. This response was impossible to lateralize due to its medial position and technological constraints on the spatial resolution of the technique. The change in rCBF in this region was proportional to the ratio of dangerous animals. The authors also noted that rCBF in the left inferior lateral prefrontal cortex (anterior to Broca's area) increased as well, but not to a statistically significant extent. In another study (also

described in Petersen et al., 1989), subjects were instructed to press a key whenever a visually-presented pair of words rhymed. Word pairs included non-rhyming, visually dissimilar pairs (dog, cat), nonrhyming, visually similar pairs (have, wave), rhyming visually dissimilar words (weigh, they), and visually similar rhymes (dog, bog). These scans were compared to those acquired while the subject maintained visual fixation on a crosshairs between pairs of words (one each above and below the crosshairs). Subtraction of the crosshairs-observation scan from the rhyme-monitoring scan suggested activation in left temporoparietal cortex "in a location near that found for auditory word input [in a previous study]" (p. 155). Interestingly, this is the only report by Petersen and his coworkers suggesting peri-sylvian activation during a language task in which the stimuli were presented visually. The presence of other areas of activation was not discussed.

An understanding of the algorithm by which these results were obtained is essential to their interpretation. First, scans were standardized to the coordinate system of Talairach, Szikla, & Tournoux (1967) as described by Fox et al. (1985). The data were then linearly normalized by dividing each pixel value by the global blood flow value. The direction and extent to which global blood flow varied between subjects or across tasks within subjects is not reported. Paired scans were then subtracted from each other on an intrasubject basis in order to isolate "the regional blood flow changes associated with the operations of each cognitive level." These "subtraction images" were then averaged across subjects in order to "increase the signal to noise ratio" of each comparison of conditions. Each average image in the 1989 study was based upon 5 - 12 intrasubject subtractions, while 8 subtractions were averaged in the 1990 study. Given the assumption that averaging the subtraction images would result in greater disparity between consistently activated areas and areas not consistently involved in the tasks, statistical significance of activated regions within each distribution (averaged subtraction image) was determined by a two step process. First, the gamma-2 statistic was used to determine if there were any significant outliers in the averaged subtraction image. If this test was significant, the magnitudes of outliers are expressed in terms of a Z score relative to the "noise level" of the distribution (response magnitude/standard deviation of the averaged subtraction image

[change scores over the standard deviation of the change scores]). Pixels with Z-scores greater than 2.17 (p>.03) are then interpreted as significant.

The methodology used in Montreal is similar in many ways (Zatorre, Evans, Meyer, & Gjedde, 1992). The principle of the subtractive hierarchy is used in the design of their studies, and analyses are based on averaged subtraction images. Unlike the St. Louis methodology, however, the Montreal group tries to link their PET data to each subject's MR data as tightly as possible. It is then parameters derived from the MR data which are used to standardize the PET data (Evans, Marrett, Torrescorzo, Ku, & Collins, 1991; Marrett et al., 1992). Although this method may be able to capitalize on MR's better spatial resolution to provide more accurate localization than algorithms based on PET data alone, it is still subject to the previously-discussed limitations inherent in any standardization of brain coordinate systems.

There are some methodological aspects of these designs to be commended. As only some of the Petersen et al. studies have been presented fully, only these may be evaluated. First, they are designed to fractionate complex cognitive acts (reading single words, in this case) and examine changes in patterns of blood flow engendered by discrete components of these acts. As such, the cognitive breakdown of tasks is generally more complete than is seen in the majority of the functional neuroimaging literature. Likewise, the investigators made a point to make the input and output demands of each task as similar as possible, thus controlling for basic processes unrelated to the cognitive phenomena of interest. In addition, the short duration of the stimulation task (not more than 90 seconds) minimizes the impact of fatigue or wavering attention.

Despite these advantages, there are a number of methodological limitations which cloud interpretation of the results. Foremost are the previously-described limitations in the interpretation of stereotactically-normalized, averaged subtraction images pertaining to the anatomical and physiological variability across brains. In addition to the limitations inherent in the analysis algorithm, however, there are also limitations in the design and report of the studies. In the 1989 study, the number of subjects upon which the each subtraction image was based was not specified. Given the authors' report that scans were based upon 5-12 intraindividual subtraction images, the number

averaged per scan used in analyses varied across conditions. Furthermore, the description of the total number of scans in the study suggests that at least a subset of subjects performed one of the stimulation tasks more than once, and the scan (or combination or scans) that was used in deriving the averaged subtraction images is not specified.

There are conceptual limitations in the design of the studies as well. These limitations have to do with the simplistic interpretation of the cognitive (and therefore neural) events occurring during each task. Petersen and his colleagues appear to take the stance that each task reflects only those processes which are *necessary* for performance of the stimulation task at hand. Thus, during visual fixation, only those areas of the brain which are necessarily involved in fixating on a crosshairs displayed in the middle of a cathode-ray tube are activated. Likewise, when "passively observing" single words, only those regions of the brain responsible for processing the visual attributes of visually presented single words are active. Clearly, this reasoning is inadequate. In fact, when one uses a resting state in which the subject is given no instruction other than to visually fixate on a given spot, one has no idea what cognitive state is being used as a "control" condition. And numerous investigations in semantic priming have shown that mere exposure to a word results in processing above and beyond the simple "visual pattern identification" level (Neely, 1991).

A summary of these findings may be found in Table 2-1. Keeping the above limitations in mind, there are a number of consistencies between the two groups of studies. First, as expected, significant increases in counts are seen in primary visual cortex regardless of the nature of the visual stimulus. Likewise, a consistent asymmetrical bilateral response is seen in temporo-occipital association cortices (perhaps Brodmann's convexity area 37) across different types of word-like stimuli, with the left side increasing more than the right. Finally, a particular region in medial extrastriate cortex (perhaps medial area 37) is consistently identified as becoming activated during the observation of orthographically-regular word forms. These results are somewhat consistent with the lesion data in alexic patients, in that damage to left medial occipital cortex has been shown to lead to an alexic syndrome that typically recovers (Greenblatt, 1983). The recovery curve is slower than could be explained by simple edemous effects on the surrounding white matter tracts, however, suggesting

Table 2-1

Summary of Lexical and Neuroimaging Findings during Visual Language Stimulation Tasks without Verbal Response, Human

Study	Stimulation Task	Control Task	Striate	Model Extrastriate	Tempo-Occipital	Posterior Superior Temporal	Inferior Lateral Prefrontal	Other
Petersen et al (1988)	Passively viewing words	Visual fixation on crosshairs	B		(L+R 50%)			L Primary
	Bigram monitoring	Visual fixation on crosshairs between words		L				
	Proportion of animals	Visual fixation on crosshairs between words						Anterior Cingulate (med)
Petersen et al (1990)	Observing false font strings	Visual fixation on crosshairs			B			
	Observing orthographically irregular strings	Visual fixation on crosshairs			B			
	Passive reading	Visual fixation on crosshairs		L	B			
	Observing regular pseudowords	Observing false font strings		L		L		
	Passive reading	Observing false font strings	B	B				A Middle Temporal
Menard et al (1996)	Passive reading	Visual fixation	B	L			L	
Bookheimer et al (1995) as cited in Posner & Raichle (1997)	Passive reading	Visual fixation		L		B	L	

Note: B denotes bilateral change in activity, L denotes change in left hemisphere, R denotes change in right hemisphere, M denotes change in a midline region.
Empty cells denote those that are not discussed, while "-" denotes areas that are not specifically identified as not changing.

that the "normal" reading system may be preferentially wired to left medial occipital regions than to the right side. However, the good recovery typically seen in these patients suggests that this asymmetrical preference may not be *necessary* to reading.

The finding of significant change in blood flow in temporo-occipital association cortex (posterior area 37, anterior area 19) is a remarkably consistent finding. The fact that rCBF in this region increased significantly every time a comparison was made between tasks involving word-like stimuli and tasks not involving these stimuli suggests that it is involved in the early in the cognitive process of reading, perhaps in direct conjunction with secondary visual cortices. This is supported by the lack of change in this region when comparing two tasks that both involve these stimuli. Recent neuroanatomical findings also support this hypothesis, as it has been shown that occipital association cortex (V4) has extensive projections to the posterior two-thirds of inferior temporal cortex in the macaque via U fibers in the white matter underlying the cortex (Tusa & Ungerleider, 1985). Rapcsak et al. (1987) postulated that this connection is important to the process of grapheme-to-phoneme conversion based on the phonological alexia exhibited by a patient with a small lobar hemorrhage in the temporo-occipital junction.

The data interpreted as pertaining to "higher" processes are less consistent between groups. Petersen and his colleagues noted an rCBF increase in the putamen when comparing passive reading to visual fixation, while Marrett and colleagues discussed an rCBF increase in left anterior temporal lobe (not further specified). Neither of these regions were replicated across labs. To date, only Petersen and colleagues have reported findings from investigations using visual word-like stimuli other than single real words as a control for visual processing demands, so these results must be interpreted with caution. Again, it should be noted that full reports of the investigations of Marrett et al. and Chertkow et al., are not available, so any mention of consistency between studies is severely limited.

Three of the findings and interpretations mentioned by Petersen and colleagues have spurred a great deal of further discussion. First is the finding that rCBF response in the anterior cingulate is related to the number of targets in an array of stimuli. This finding has been expanded upon in investigations of attention which are beyond the scope of this review (Posner & Petersen, 1990). The

second finding is the increase in rCBF in left posterior superior temporal gyrus during the rhyme monitoring task. Since this was the only subtraction using visual stimuli that showed a response in this area, this was interpreted as an area important to the phonological monitoring of single, visually presented words. This interpretation is consistent with the performance of patient H.R. (Friedman & Kohn, 1990), who evidenced significant difficulties with a number of rhyming tasks. CT on H.R. suggested a patchy lesion involving the temporal isthmus, the posterior half of Wernicke's area, and the posterior supramarginal and angular gyri.

The finding which has produced the greatest controversy in the studies of language comprehension is the increase in rCBF in the inferior lateral prefrontal region during the reading of real words. At first glance, the 1989 and 1990 conclusions of Petersen and colleagues about this issue seem contradictory. In the 1989 study, the investigators showed no activation of the left inferior lateral prefrontal region (Brodmann's areas 45, 47) when subtracting the rCBF pattern engendered by fixating on a crosshairs from the pattern engendered by silently reading real words. In contrast, this region was shown to increase significantly when subtracting the rCBF pattern engendered by fixating on false font strings from that engendered by reading silently. A plausible explanation offered by Petersen (personal contact) to explain this apparent contradiction is that there was a great deal of variability in the subtraction image generated when comparing the reading and rest conditions due to the extreme increase in activity in the occipital and temporo-parieto-occipital regions. As such, the relatively modest increase seen in left inferior lateral prefrontal cortex was "washed out." When the activity related to visual processing was "controlled" by comparing reading silently to observing strings of false font characters, the same response in the inferior prefrontal region was comparatively strong enough to reach statistical significance. This response is taken by the authors to indicate that the left inferior prefrontal region is involved in semantic processing that occurs during reading. This interpretation will be discussed further after presenting evidence related to the auditory comprehension of single words.

Aphasic Deficits in Spoken Word Comprehension

One way of increasing one's confidence about those regions which may be involved in single word comprehension is to consider the findings of studies using aural presentation of single words. Comprehension of the spoken word has received a great deal of attention in the aphasia literature and, in fact, has been shown to fractionate in a manner similar to that seen in single word reading (Ellis & Young, 1988). The comprehension of single spoken words may be broken down into (1) the perception of the sound pattern, (2) the decoding of this pattern into identifiable phonemes, (3) identification of the sequence of phonemes as a lexical entry, and (4) accessing the semantic information associated with the identified lexical entry. Again, examination of the available data suggests that current functional neuroimaging technology is probably not capable of making the fine discriminations necessary in dissociating lexical identification and semantic access in a normal population, so this review will knowingly commit the error of referring to these as a unitary construct to be referred to as "lexical-semantic processes."

The phonological and lexical-semantic components of spoken word comprehension have been shown to dissociate in pathological populations. The syndrome of "pure word deafness" reflects an impairment in the phonemic decoding of the auditory language stream. Although the hearing of patients with pure word deafness is within normal limits, these patients have extreme difficulty understanding spoken language, despite intact comprehension of written language and normal expressive language. This syndrome has been broken down into two relatively distinct syndromes (Auerbach et al., 1982; Kertesz, 1983). The first type, commonly associated with bilateral superior temporal lobe lesions, is marked by deficits in the general ability to properly sequence perceived sound patterns (Auerbach et al., 1982). The second subtype, conversely, is typically seen after unilateral lesions in the dominant periauditory cortex and is more specifically linked to difficulties in linguistic auditory discrimination (Saffran et al., 1976).

In contrast to pure word deafness, patients with transcortical sensory aphasia (TCSA) have no difficulties decoding the stream of language, as evidenced by their normal repetition. However, these patients have profound difficulties with language comprehension, and expressive language is marked by fluent but semantically empty speech. This behavioral syndrome may be the result of a number of

different etiologies, from dementia of the Alzheimer's type to infarction of the left temporo-occipital junction (Alexander, Hiltbrunner, & Fischer, 1989). In fact, some data suggests that there are distinct subtypes of TCSA which dissociate according to the functional system(s) left intact to handle repetition (Coslett, Roeltgen, Rothi, & Heilman, 1987). The behavioral and pathophysiological variability manifested by patients with this syndrome complicate the process of identifying the neuroanatomic correlates responsible for the observed deficits. However, analysis of the available data from a number of sources suggest that it may be the function of the dominant inferolateral temporo-occipital cortices and the regions that integrate this region with other functional subsystems (i.e. pathways in the posterior periventricular white matter adjacent to the posterior temporal isthmus) that are critical in the manifestation of TCSA (Alexander et al., 1989). The individual behavioral manifestation of each case of TCSA may be a function of the parameters of the pathology within these regions (Coslett et al., 1987).

The most pervasive disturbance of language comprehension is seen in Wernicke's aphasia, a syndrome in which comprehension, repetition, and expressive speech are all severely impaired. Expressive speech is fluent but marked by frequent semantic and phonemic paraphasias, often deteriorating to jargon. This syndrome is typically seen following damage to the temporoparietal junction, with the posterior third of the posterior superior temporal gyrus (Wernicke's area) typically involved. The increased frequency of receptive and expressive phonological difficulties in Wernicke's aphasia relative to TCSA suggests that the temporoparietal junction plays an important role in both the morphological decoding of the incoming language stream and the conceptual morphological encoding necessary to expressive language. The frequency with which one sees semantic paraphasias after damage to this region also suggests some role in lexical-semantic processes. A number of studies have been done in an attempt to disambiguate the phonological-morphological functions of the region from the lexical-semantic processes (Cappa, Cavalotti, & Vignolo, 1981; Kertesz, 1983). The results of these studies are not crystal clear, however. On the one hand, some data has been presented which suggests that phonological-morphological processes are impacted in proportion to the involvement of the supramarginal gyrus in addition to the posterior superior temporal region, while lexical-semantic

deficits are more heavily affected when the lesion is slightly more ventral and posterior (Cappa, Cavallotti, & Vignolo, 1981; Kertesz, 1983). These positions seem to be supported by the findings that conduction aphasics, in whom phonological processing is clearly impaired, typically have lesions in the region of the supramarginal gyrus, while transcortical sensory aphasics have the semantic difficulties and inferolateral temporo-occipital lesion locus described earlier. On the other hand, recent findings suggest that deficits in semantic comprehension of single words is most strongly tied to pathology of the dominant posterior superior temporal and inferior parietal cortices (Wernicke's area and supramarginal gyrus) in patients with single left-hemisphere CVA's (Hart & Gordon, 1990). Thus, the posterior third of the dominant superior temporal gyrus appears to play a primary role in lexical processes underlying the comprehension of language. As will be shown, this consistency has received mixed support from the functional neuroimaging literature examining language comprehension in normal individuals.

<u>Functional Neuroimaging of Spoken Word Comprehension</u>

A number of functional neuroimaging studies have examined the comprehension of single spoken words. Bartlett, Brown, Wolf, and Brodie (1987) measured regional cerebral glucose metabolic rates (rCMR) in two groups of right-handed normal males in an investigation of regional intercorrelation during single word monitoring. The language stimulation group was notably older than the control group (mean ages 40.8 and 28.4, respectively). The 17 control subjects were scanned lying quietly on the scanner table with the eyes open and their ears plugged. The 12 language stimulation subjects were presented with monosyllabic English words at a rate one every 3.7 seconds and instructed to make a foot movement every time they heard the phoneme /b/ or /s/. Seven of the subjects were instructed to make this movement on the left, while five made it on the right. The eyes of the language stimulation group were closed throughout the stimulation.

Thirty regions of interest (ROI's) were identified using a combination of a neuroanatomical atlas, superimposition of images, and experimenter judgment in order to get ROI's with the highest metabolic rates and smallest regional standard deviations. ROI's were then averaged into six peri-

sylvian (left and right inferior frontal, superior temporal, and lower temporal), six control (left and right anterior superior frontal, posterior temporal, occipital), two motor response (left and right mesial sensorimotor areas associated with foot and leg movement), and two subcortical regions (left and right thalamus). Given the thickness of the slices examined and the lack of specific description of localization, finer identification of the regions examined is not possible.

Interregional relationships were explored using partial correlations (i.e. correlations controlling for mean whole-slice value). In the unstimulated subjects, significant relationships were found between left and right anterior superior frontal regions (roughly areas 9 and 46: $r = .84$), left and right Broca's area ($r = .70$), left and right occipital cortex ($r = .72$), and left thalamus with right Wernicke's area ($r = -.66$). Significance was determined utilizing Bonferroni's procedure due to the high number of correlations. In the stimulated subjects, a number of areas were found to be significantly correlated with left Broca's area, including left Wernicke's area ($r = .88$), right Wernicke's area ($r = .87$), left Heschl's gyrus ($r = .75$), left anterior superior frontal ($r = .87$), right anterior superior frontal ($r = .83$), and left parieto-temporal cortex ($r = .78$). In addition, significant relationships were found between left and right Wernicke's areas ($r = .86$), left and right anterior superior frontal ($r = .87$), left frontal and right Wernicke's ($r = .79$), left and right occipital cortex ($r = .84$), and left and right sensorimotor cortex ($r = .86$ roughly face region). Mean metabolic values were consistently lower in stimulated subjects, while standard deviations of regional means were higher. Unfortunately, interpretation of these findings is complicated by the finding that stimulated subjects were significantly older than the unstimulated subjects, and regional metabolism has been shown to decrease with age (Martin, Friston, Colebatch, & Frackowiak, 1991). Although a comparison of simple correlations and partial correlations with age as the independent variable suggested that age played little role in influencing the relationships between regions, it is unclear how age interacted (if at all) with stimulation in contributing to the lower rates of metabolism in the stimulation task.

Petersen and his colleagues performed a number of studies analogous to those using visual stimuli (Petersen et al., 1989). Only one of these studies was aimed at elucidating which areas are involved in the "passive auditory perception" of single words (nouns). In this study, subjects were

required to visually fixate on a crosshairs and either remain in a resting state or listen to nouns presented at 1 Hz. Results of the averaged-image subtraction suggested bilateral increases in primary auditory cortex and unilateral increases in left anterior superior temporal cortex (just below the Rolandic fissure), left temporoparietal cortex, and inferior anterior cingulate cortex. The authors also reported activation in the right superior temporal region slightly posterior to primary auditory cortex. Of these regions, the greatest increases were seen in right primary auditory cortex, right posterior superior temporal cortex, and left temporoparietal cortex.

A more detailed breakdown of auditory comprehension was performed in Montreal by Zatorre, Evans, Meyer, & Gjedde (1992). Using a subtraction methodology, these investigators had subjects perform a number of tasks: (1) recline silently, (2) press a key to alternate pairs of noise bursts (noise condition), (3) press a key to alternate pairs of consonant-vowel-consonant syllables (passive speech condition), (4) press a key when the syllables ended with the same phoneme (phonetic condition), (5) press a key when the second syllable had a higher pitch than the first (pitch condition). The same syllables were used in tasks 3, 4, and 5. Subtraction of the resting baseline from the noise condition showed bilateral increases in activity in primary auditory cortex, unilateral increases in left sensory-motor hand area, left anterior superior temporal gyrus, and right lateral cerebellum, and midline increases in supplementary motor cortex and anterior cingulate cortex. Subtraction of the noise condition from the passive speech condition showed bilateral increases in anterior superior temporal gyrus and unilateral increases in right anterior superior temporal gyrus (more anterior than the bilateral focus) and left inferior prefrontal cortex (anterior to Broca's area). Subtraction of the passive speech condition from the phonetic condition showed unilateral increases in left Broca's area, "near the superior aspect of the supramarginal gyrus," left inferior temporal gyrus, and the right occipital pole in addition to midline increases in anterior and posterior cingulate cortex. Finally, subtraction of passive speech from the pitch condition showed unilateral increases in the right inferior and middle frontal gyri and left SMA in addition to increases in midline occipital cortex.

The group of investigators based at Hammersmith Hospital in London has also been active in the investigation of single-word processing. Wise and his colleagues (Wise et al., 1991) had subjects

perform four tasks: (1) rest, during which subjects were instructed to "empty their minds," (2) listen to nonwords conforming to typical English phonological structure, (3) decide whether two aurally-presented nouns were correctly categorized and signal this decision by opposing the thumb and the forefinger of the left hand, and (4) decide whether a noun and a verb were correctly categorized, as in task 3. In order to control for the decision to signal and its action as behavioral variables between conditions, subjects were instructed to oppose their left thumb and forefinger every few seconds in the rest and nonwords tasks. For the first three subjects, nonwords were presented at a rate of 40 per minute (wpm), while 13-15 noun-noun or verb-noun pairs were presented per minute. For the last three subjects, the rates were 60 wpm and 25-27 pairs per minute, respectively. In the categorization tasks, all subjects achieved 95% or greater accuracy, although the authors do not report if this figure varied by stimulus presentation rate. Results showed virtually identical patterns of activity when comparing the nonword, noun-noun categorization, and verb-noun categorization tasks to the resting baseline. This pattern involved bilateral rCBF increases in Heschl's gyrus, posterior superior temporal cortex, and middle superior temporal cortex. Direct comparisons of (1) the noun/noun and noun/verb categorization conditions with the nonword condition, and (2) the categorization conditions to each other yielded no significant differences. In addition to the comparisons of the different tasks to each other, the authors examined the correlations between the percentage increase in rCBF in the superior temporal regions and the frequency of stimuli presentation. Significant positive correlations with presentation rate were found bilaterally with rCBF in Heschl's gyrus and middle superior temporal gyrus and unilaterally the right posterior superior temporal region (all $p<.01$). Conversely, the correlation between presentation rate and rCBF in the left posterior superior temporal region did not reach statistical significance ($r=.36$, $p<.08$).

In a chapter reviewing PET investigations of language in normal subjects (Wise et al., 1991), Wise and his colleagues anecdotally report a number of other investigations that have been carried out in their lab as well. One of these has particular relevance to the comprehension of single words. The pattern of activation seen while listening to reversed English words was compared to that seen during the previously-described resting state. This comparison reportedly led to a pattern of change virtually

identical to that seen in the comparisons performed in the previous study (Wise et al., 1991a): that is, bilateral activation of Heschl's gyrus, middle superior temporal gyrus, and posterior superior temporal gyrus.

In evaluating the value of these studies, it is important to keep in mind the advantages and limitations of the techniques. These same considerations described earlier apply to the St. Louis and Montreal studies. In addition, Zatorre and coworkers failed to provide information about the rate at which subjects performed the different tasks. Since this appeared to be dependent upon subject reaction times, the impact of this factor on the amount of processing required of each subject across tasks is unknown. It is also important to note that the Hammersmith group uses a slightly different imaging algorithm than that employed at St. Louis and Montreal, so this will be briefly reviewed. In concordance with the St. Louis and Montreal studies, the Hammersmith images were standardized for size and shape to the coordinate system of Talairach & Tournoux (1988). The methodology used by this group is detailed by Friston et al. (1989). However, instead of subtraction of averaged scans from each other, data were analyzed via analysis of covariance (ANCOVA) with global blood flow as the covariate. This was strategy was based on the finding of Friston and his colleagues (1990) that the relationship of global blood flow to rCBF may vary across regions. In this strategy, each pixel in the standardized coordinate system is analyzed via ANCOVA, and the resulting adjusted mean scores are compared with pre-planned t-tests. The total number of pixel-by-pixel comparisons required to examine the entire brain is approximately 147,000 (Friston, Frith, Liddle, & Frackowiak, 1991). The resulting t-statistics are then presented as a *statistical parametric map* (or SPM). The number of significant t-statistics is then compared to the number expected by chance with Bartlett's χ^2. If the number of significant t-tests is significantly greater than would be expected by chance, individual pixels are then interpreted (Friston et al., 1991).

There were a number of good points about the methodology used by Wise and colleagues. First, they are the only group to date to attempt to systematically investigate the effect of presentation rate on changes in rCBF in a task using aural stimulation. Furthermore, the study employed a direct

comparison of conditions rather than a subtraction methodology, this avoiding the interpretive complications inherent in averaged subtraction images.

Although the use of ANCOVA may be an advance to account for the variability across regions, the technique has a number of limitations. In deriving their SPM's, the authors smooth their data in order to account for interindividual differences in gyral anatomy." Smoothing is a function whereby each pixel x comes to represent the average of the pixels in a predefined radius from the pixel x. In the Friston et al. methodology, the degree to which this smoothing "blurs" the data varies according to the statistical properties of the distribution of the images being examined. In addition, in order to ascertain which areas were significantly activated, the authors compared "average images" for each condition, rather than obtaining values for each individual brain. Given that the authors had "standardized" their individual images and that their design anticipated analyses of certain regions *a priori*, it is unclear why rCBF values were not obtained from individual scans using the same algorithm used to locate pixels on the average images and then analyzed. Given the variability which will remain in exact localization even after standardization (Steinmetz & Seitz, 1992), obtaining values from average images may impact upon the findings in any number of ways. Since no data were given about the variability in the average scans, it is difficult to estimate what this effect may have been. There were other limitations to the study as well. First, it was reported that the first author was one of the subjects. Thus, one wonders how familiar the subjects were with the hypotheses and stimuli of the study, and what effect this may have had on their performance of the tasks. Another issue clouding interpretation of the data is the fact that, although the issue of disentangling stimuli presentation rate from type of stimuli in affecting rCBF is an important one, the division of the six subjects into two groups of three varying on stimulus presentation rate raises some concern. In particular, even though the authors showed that increased presentation rate led to higher flow in 5 of 6 superior temporal areas, these two groups of three were combined in drawing between-task conclusions. Also, different tasks called for substantial differences in output, as the motor response would increase by approximately 33% in the 60 stimuli/minute condition. Given that the authors only reported the correlations between the rate of presentation and changes in percentage increase for superior temporal regions, it is unknown

if and to what extent varying presentation (and thus output) rates affected any other areas. Thus, the effect that this combination of images may have had on the pattern of results is uncertain. Finally, the tasks were administered to each subject in the same order, thus making an order effect on the results impossible to rule out.

A summary of the results regarding the comprehension of aurally presented words is found in Table 2-2. There are a number of interesting consistencies across studies. First, for the most part, primary and secondary auditory cortices area are affected in predictable ways by auditory stimuli. The exceptions are (1) Zatorre's finding of increase limited to the left side when comparing alternating noise bursts to rest, and (2) the consistent lack of change in primary or secondary auditory cortices when comparing vocal tasks to rest. It seems as if the cortical response to one's own speech does not activate the language comprehension system in the same way that externally-generated language does. Another relatively stable finding across laboratories is an increase in rCBF in the left posterior superior temporal/temporo-parietal region whenever language is perceived at the phonemic level. Finally, the functional breakdown performed by Zatorre and colleagues suggests a role for both Broca's area and the superior portion of the supramarginal gyrus in tasks which require careful monitoring of phonemic information.

Most of the above results are consistent with what would be expected from the lesion literature. The early activation of primary and secondary auditory cortices may be reflective of some of the processes impaired in pure word deafness, while the consistent involvement of the posterior superior temporal regions/temporoparietal junction at the morphemic level is consistent with the analyses that are known to break down in patients with lesions in this region. Furthermore, Zatorre and colleagues' report of activity in Broca's area and superior supramarginal gyrus during phonological monitoring is not inconsistent with the phonological deficits seen in conduction aphasia. This syndrome has been associated with lesions in the connections between the temporoparietal junction and the inferior premotor cortices (Wernicke, 1874). A lesion in the region of the supramarginal gyrus has been hypothesized to disrupt the connection between these cortices. In addition, recent data suggest that while the classically defined arcuate fasciculus is a primary pathway between these two regions,

Table 2-2

Summary of Functional Neuroimaging Findings during Auditory Language Stimulation Tasks with no Verbal Response Detected

Study	Stimulation Task	Control Task	Primary Auditory Cortex	Posterior Superior Temporal	Inferior Frontal	Inferior Lateral Prefrontal	Anterior Temporal	Anterior Cingulate	Other
Wioland et al. (1999)	Passive listening to single words	Visual fixation on crosshairs	B	R	L	–	L	M (indirect)	R Primary Motor (hand), R Lateral Cerebellum, R M1/SMA, L Middle Temporal
Zatorre et al. (1992)	Press a key to alternate noise bursts	Rest for silently	L	R	–	–	–	M	L Broca's area, L Inferior Parietal, L Superior Temporal, R Occipital Pole
	Press a key to alternate syllables	Press a key to alternate noise bursts	L	L	–	–	–	K (2 foci at Brodmann's areas 7/22 and 38)	R Middle Temporal Gyrus
	Press a key when last phoneme identical	Press a key to alternate syllables	–	B	–	–	R	–	M (also a posterior cingulate focus), L Inferior Parietal
	Press a key when initial pitch higher	Press a key to alternate pitch triplets	–	R	–	–	R	R	R Middle Frontal Gyrus, L SMA, M Occipital
Wise et al. (1991a)	Listen to repeatedly, oppose left thumb and forefinger every few seconds	Rest for silently, oppose left thumb and forefinger every few seconds	B	B	B	–	–	–	R Middle Superior Temporal
	Oppose left thumb and forefinger if two nouns are semantically related	Rest for silently, oppose left thumb and forefinger every few seconds	B	B	–	–	–	–	R Mid-Superior Temporal
	Oppose left thumb and forefinger if a noun and a verb are semantically related	Rest for silently, oppose left thumb and forefinger every few seconds	B	B	–	–	–	–	R Mid-Superior Temporal
	Oppose left thumb and forefinger if two nouns are semantically related	Listen to reversals, oppose left thumb and forefinger every few seconds	–	–	–	–	–	–	–
	Oppose left thumb and forefinger if a noun and a verb are semantically related	Listen to reversals, oppose left thumb and forefinger every few seconds	–	–	–	–	–	–	–
	Oppose left thumb and forefinger if two nouns are semantically related	Oppose left thumb and forefinger if a noun and a verb are semantically related	–	–	–	–	–	–	–

Note: B denotes bilateral change in activity, L denotes change in left hemisphere, R denotes change in right hemisphere, M denotes change in a midline region. Empty cells denote those that are not discussed, while "–" denotes areas that are specifically identified as not changing.

there are at least one other pathway running beneath the insular cortex in the extreme capsule (Damasio & Damasio, 1983). Thus, it is conceivable that the projections into both parietal cortex and inferior premotor cortices may become activated during the normal process of attending to phonemic attributes of syllables. An important difference between the findings of Zatorre et al. and those in the lesion literature is the locus of activity in the supramarginal gyrus. Zatorre et al. reported activation in the superior portion of this region, while the lesion literature suggests a more inferior focus is important to the phonological processing of language. As Zatorre et al published no figures showing the region of activation, it is difficult to know if (a) there was overlap with inferior supramarginal cortex, (b) there was close enough proximity to inferior supramarginal cortex to attribute the discrepancy to localization limitations inherent in standardized images, or (c) the finding of Zatorre et al was simply contradictory to what would be expected from the lesion literature.

As mentioned earlier, the potential role of the inferior lateral frontal prefrontal cortex (areas 45, 47) during language comprehension has received a great deal of recent interest (Carr, 1992; Compton, Grossenbacher, Posner, & Tucker, 1991; Damasio & Damasio, 1992; Posner & Carr, 1992). As the reader will recall, Petersen and his colleagues noted an increase in activity in this region during the reading of real words in their paradigm using visual stimuli once the response attributed to primary sensory processes had been "controlled." Although Petersen and colleagues have yet to control the primary sensory processes in a paradigm using auditory stimulation, Zatorre and colleagues (1992) performed an analogous comparison when subtracting "alternating noise bursts" from "alternating syllables." This comparison also engendered an increase in rCBF in the left inferior lateral prefrontal region anterior to Broca's area. Both of these groups have related this response to semantic processing. Wise and colleagues, on the other hand, cite their data to dispute this claim. This group found no significant changes in the inferior lateral prefrontal cortex in any of their comparisons. They maintain that their data support the role of left posterior superior temporal gyrus (Wernicke's area) in the comprehension of language. They explain the activation of left posterior superior temporal gyrus during the monitoring of nonwords as being due to the conceptual dynamics proposed in parallel distributed processing models of language comprehension (Rumelhart & McClelland, 1986), in which

it is posited that comprehension is arrived at though the emergent realization of the auditory pattern of the word. Theoretically, the cortices (or neural networks) involved would automatically engage in many of these processes regardless of the nature of the linguistic stimuli perceived; in the case of real words, the network concerned with lexical identification would settle into a coherent pattern of activity, while the attempted comprehension of a nonword would activate the same network (concerned with lexical identification) but would not settle into a coherent pattern of activity.

Examination of the lesion literature supports neither position strongly. As noted above, Wernicke's area proper does not appear to be strongly implicated in the semantic processing of visual or auditory input strings beyond the phonemic or possibly even lexical level. Likewise, there is very little lesion literature to support a role for Brodmann's areas 45 and/or 47 in semantic processing. The pair of studies from outside the functional neuroimaging literature that are frequently cited to support this role are those by Milberg, Blumstein, & Dworetzky, which explore the way in which semantic primes affect the response times and accuracy of Broca's and Wernicke's aphasics in lexical decision tasks (Milberg & Blumstein, 1981; Milberg, Blumstein, & Dworetzky, 1987). The results of these studies suggest that, while Broca's aphasics are more accurate in their lexical decisions than are Wernicke's aphasics, their response times do not show the expected effects of semantic cuing. Wernicke's aphasics, on the other hand, benefit from semantic primes in a pattern similar to that shown by normals. An obvious limitation of using these studies as support for the findings of Petersen et al. and Zatorre et al. is that Broca's aphasia does not necessarily imply a lesion in the inferior lateral prefrontal cortex, and, in fact, examination of the CT data cited by Milberg and colleagues suggests that less than half of the Broca's aphasics had structural lesions in this area. Specifics as to when these scans were acquired were not presented, however, and structural imaging techniques such as CT are limited in their ability to delineate "functional" lesions as defined by hypometabolism (Metter et al., 1986). Thus, such a lesion cannot be ruled out in most of Milberg et al.'s patients; however, the relationship between the anatomical focus defined by Petersen and colleagues (1990) and the sites of lesions explored by aphasia investigations to date is far from clear. Another limitation in the interpretation of these findings as suggesting a role for Brodmann's areas 45 and/or 47 in semantic

processing emerges from the work of Goldman-Rakic and colleagues (1992). Briefly, the work of these authors indicates that the prefrontal cortex is important to working memory, and the methods used by Milberg, Blumstein, and colleagues do not allow one to rule out the possibility that one is observing the consequences of an impairment in working memory (i.e., difficulty establishing or maintaining an internal representation to guide further responses) rather than an impairment in semantic processing.

Thus, an integration of the functional neuroimaging and lesion data concerning the comprehension of the written or spoken single word leaves many questions unanswered. Foremost among these questions is the role of the inferior lateral prefrontal region in single word comprehension. To date, the data seem to support different interpretations depending on the modality of the stimulus, and neither of the available interpretations are particularly well supported by the lesion literature. Another interesting issue arising from comparing the two literatures is the striking lack of perisylvian activation during language tasks mediated by visual stimuli. Although posterior area 37/anterior area 19 seems to be consistently involved, the response in this appear to be more related to visual processing than to language per se, although the apparent asymmetry favoring the left suggests some degree of specialization. In addition, anecdotal reports by Raichle (1991) suggest that a change in presentation rate dramatically increases the response in posterior superior temporal cortex, suggesting that methodological factors may well play a role in the data that is acquired. Examination of the available data, then, suggests that the lack of consistent perisylvian response may be due largely to (1) lack of control of primary sensory responses, which have consistently been shown to be much greater than responses related to the "higher functions" involved in the comprehension of language, and (2) time-linked variables, such as the rate of stimulus presentation.

Aphasic Deficits in Language Production

The generation of language may be conceptualized as involving (1) the drive to generate language, (2) the formulation of the concept to be communicated, (3) the identification of the open-class lexical items appropriate for communicating the concept, (4) the manipulation of the morphology

of these open-class lexical items and the relationships between them in order to precisely communicate the concept, (5) the programming of the phonological sequences necessary for communication of the formulated message, and (6) motor execution of the phonological program. These steps are not seen as a strictly linear sequence but rather as psycholinguistic subcomponents which must be accomplished in some manner during the production of language. The dissociation of the first three components is remarkably difficult to do in a normal population, and is probably far beyond the current capabilities of functional neuroimaging due to its apparent difficulties in discriminating between tasks with relatively subtle differences in cognitive demands. Thus, although all of these components are important in the production of language, the lexical-semantic, grammatical, and phonological components of this process are those with which this study will directly address. For the purposes of this study, the lexical-semantic component may be seen as a combination of steps 2 and 3, the grammatical component as step 4, and the phonological as step 5. These will be reviewed after briefly discussing the general issue of generativity.

As discussed earlier, the production of language may be viewed on a continuum defined by the amount of novel language formulation required. Fundamental to this formulation is the drive to generate language. A few studies in the lesion literature have addressed this issue, primarily with regards to dynamic and transcortical motor aphasic syndromes. Dynamic aphasia, a term coined by Luria, may be defined as a selective impairment of this drive in the relative absence of other language impairment (Luria, 1970). In its most selective form, this impairment seems to be most strongly tied to lesions in superior medial frontal regions (SMA) and their connections to dorsolateral frontal cortices (Alexander, Benson, & Stuss, 1989). It is lesions in these same regions, anterior and superior to Broca's area, that have been tied most strongly to transcortical motor aphasia. In this syndrome, fluency of spontaneous speech is also impaired; however, the clinical picture is usually more complex, in that greater impairment is typically seen in syntactic function and occasional paraphasias are noted. Notably, decreases in "verbal fluency," or the ability to generate words beginning with a given letter, have been repeatedly shown to be associated with lesions in left dorsolateral frontal cortex (Benton, 1968; Miceli et al., 1981; Pendleton et al., 1982), although findings also suggest this deficit is also seen

in patients with nonfrontal lesions (Pendleton et al., 1982). An important aspect to both of these clinical syndromes is the preservation of repetition and the relative sparing of the semantic integrity of the language formulation.

Lexical-semantic processes in the production of language are tied more closely to lesions in the posterior cortices. Typically, selective impairments in these functions are seen only in TCSA, while striking impairment is seen in conjunction with greater difficulty in phonological processes in Wernicke's aphasia. The previous discussion of the psycholinguistic and pathophysiological mechanisms underlying each of these syndromes discussed their impact on the generation of language.

Impairment in the grammatical formulation of language has received increasing attention throughout the past 20 years. Initially, this impairment was felt to be one of the hallmarks of Broca's aphasia (Goodglass & Menn, 1985). However, traditional conceptualizations of Broca's aphasia have undergone intense scrutiny during the past two decades. While the classic Wernicke-Lichteim model of language hypothesized the inferior foot of the third frontal gyrus (Broca's area) to play a critical role in the phonological and grammatical formulation of language, recent findings have suggested that the traditional syndrome of Broca's aphasia (sparse, effortful, dysfluent agrammatic speech with relatively spared comprehension) is composed of a number of mutually dissociable components whose neural instantiation may have little if anything to do with Broca's area (Alexander, Naeser, & Palumbo, 1990; Nadeau, 1988). With regards to grammatical formulation in particular, impairments in expressive grammar have been seen in aphasic patients with both anterior and posterior lesions (Blumstein, 1988). However, on closer inspection, these grammatical impairments appear to differentiate into impairments at the sentential level (difficulties with *syntax*) and impairments at the inflectional morphological level (difficulties with *concatenation*) (Nadeau, 1988). Some recently presented data suggest that syntactic difficulties appear to be preferentially bound to damage in the anterior cortices, while concatenation difficulties appear to be more strongly bound to damage in the perisylvian regions (Kolk, van Grunsven, & Keyser, 1985; Nadeau, 1988).

Similarly, as mentioned in the previous discussion of Wernicke's aphasia, current evidence does not support the notion that Broca's area is solely responsible for the phonological coding of

spoken language. This notion is critically flawed in two respects: (1) lesions in the posterior superior temporal gyrus disrupt phonological aspects of output despite spared anterior cortices, and (2) there have been a number of case reports of patients with lesions including Broca's area that have no demonstrable deficit in expressive language (Alexander et al., 1990; Mohr et al., 1978; Nadeau, 1988). Relatedly, the majority of patients diagnosed as Broca's aphasics have lesions incorporating insular, anterior parietal, and subcortical regions in addition to their underlying white matter pathways (Mohr et al., 1978). In effect, given the extent of the damage typically seen in Broca's aphasia, and the fact that many lasting Broca's aphasias which have resolved into this syndrome, the traditional syndrome of Broca's aphasia may be in fact no more than the representation of the right hemisphere's relative ineptitude at handling phonological and syntactic function (Baynes, 1990). Rather, the behavioral manifestations of the transcortical aphasias make a strong argument that it is the perisylvian cortices, not the anterior cortices, that support the processes fundamental to phonological decoding and encoding of language, as preservation of the perisylvian regions typically preserves repetition despite potentially pervasive pathology across other aspects of language functioning.

Investigation of the strongly-mediated generation of language in normals with functional neuroimaging has typically been conducted by having subjects perform tasks that are devised require differing amounts of novel formulation of language. Thus, tasks conceptualized as "low-level" include repetition and automatic language. This may be problematic, as both repetition and automatic language have been shown to dissociate from other aspects of language. In transcortical mixed aphasia, these may be the only two sorts of clear verbalizations available to the patient, while even global aphasics generally show relatively good retention of at least some aspects of automatic language. Thus, it may well be that these sorts of productions disproportionately rely on neural substrates that are relatively peripheral to normal language generation. If this is the case, the studies employing this sort of hierarchy may not be looking at the hypothesized additive hierarchy but rather at a hierarchy that incorporates qualitatively (and neurally) different processes at different levels. Nevertheless, as some aspects of language are certainly required for these productions (such as

phonological programming), this review will incorporate the studies which have examined these functions in order of increasing demand for novel language formulation.

In 1974, Ingvar and Schwartz's SPET investigation of changes in rCBF in the left hemisphere during automatic speech marked the beginning of functional neuroimaging studies of normal language. One of the comparisons made by these authors was between a resting control state and a task in which subjects were instructed to recite either the months of the year or the days of the week. The authors noted no significant changes in global blood flow between conditions, but regional increases were observed throughout most of the frontal cortex and in the superior parietal regions. Likewise, increases in rCBF were observed in the middle and anterior portions of the temporal lobe. In contrast, rCBF decreased in the occipito-parietal-temporal region. Larsen, Skinhøj, and Lassen followed this study in 1978 with a more detailed look at automatic speech. These investigators compared rCBF patterns during (1) rest, and (2) counting from 1 to 20 or reciting the days of the week at a rate of one word per second. Localization was performed by using three external markers and the proportional system of Talairach et al. (1967). These investigators found a significant increase in right hemisphere flow (mean average increase 10%) and no difference in left hemisphere flow (mean average increase 3%). Bilateral regional increases were seen in SMA, the face sensorimotor region, and the posterior superior temporal region. On the left side, increase in SMA flow was more pronounced, and face sensorimotor and temporal regions of activation were more distinct from each other. Bilateral regional decreases were seen in parietal regions. An analysis of repeated measurements on a subset of patients revealed the same pattern of activation with a decrease in the magnitude of change from rest to speech. The poor resolution of the images acquired in these studies precludes further anatomical specification of the regions of interest.

As the SPET technique used in these studies is substantially different from the previously reviewed PET techniques, it is important to keep in mind a different set of limitations to the interpretability of these studies. The most obvious of these is the nature of the experimental samples. Ingvar and Schwartz's sample consisted of ten or eleven psychiatric patients "with normal neurological findings." The data show ten subjects, but eleven are described. Five were chronic schizophrenics,

two had recent manic episodes, and one each had "endogenous depression," alcohol abuse (dry at the time of the experiment -- it is unclear for what period of time), "chronic lymphadenopathy of uncertain etiology," and depressive symptoms following a mild head injury. The medication status of the subjects was not discussed. Likewise, the sample that Larsen and colleagues used had clinical symptoms sufficient to warrant clinical angiography, and an unspecified number of subjects received "a small dose of diazepam."

As discussed earlier, the SPET technique has its limitations as well. Both studies were extremely invasive, as all of the subjects received their isotope (3-5 mCi of ^{133}Xe) into their cannulated internal carotid artery (side not documented), and seven of Ingvar and Schwartz's subjects also had the jugular vein cannulated. Although Larsen et al's study had greater localizing power due to a greater number of cameras, it is important to keep in mind that the detectors used in these studies are "looking straight through" the brain. Although these detectors measure the activity in the outer third three times as effectively as the inner third (Risberg, 1980), the extent to which subcortical structures contribute to the observed levels of activity is uncertain. A number of mathematical models have been derived to minimize the impact of this problem (Risberg, 1980); however, the most effective of these were not employed in these studies. Finally, the measurement of only one hemisphere in each subject makes it difficult to disentangle the contributions of regional and global changes to the asymmetry observed in the sample of Larsen and colleagues.

A summary of the findings of these two studies may be found in Table 2-3. Technological limitations make interpretation of these studies beyond a gross level difficult. The consistent data from the two studies suggest that the generation of automatic language is marked by an increase in rCBF in SMA (particularly on the left) and a decrease in rCBF in the temporo-parieto-occipital association cortices. The SMA increase is consistent with what would be expected from the lesion literature, while the lesion literature does not speak directly to the temporo-parieto-occipital decrease. Given the similarities of the stimulation and control tasks used in the two studies, it is difficult to determine what sorts of differences in cognitive processes would account for the different conclusions about changes in other regions. Examination of the reports of the two studies suggests that these differences may be

Table 2-3
Summary of Functional Neuroimaging Findings during Automatic Language Stimulation Tasks

Study	Stimulation Task	Control Task	Ventral Operculum	Broadmann Prefrontal	Inferior Lateral Prefrontal	Medial Superior Frontal (SMA)	Posterior Superior Temporal	Temporo-Parieto-Occipital	Other
Ingvar & Schwartz (1974) (NON X-RAY HEMISPHERE STUDIES)	Recite days of the week or counts of the year	Recline quietly with eyes closed	L	L	L	L			Motor and Sensory, Temporal, Superior Frontal
Larsen, Skinhøj, & Lassen (1978)	Count from 1 to 20 or recite days of the week	Recline quietly with eyes closed	B		B	B	B (decrease)	B (decrease)	B Sensorimotor Face & Hemisphere

Note. B denotes bilateral change in activity, L denotes change in left hemisphere, R denotes change in right hemisphere, M denotes change in a midline region. Empty cells denote those that are not discussed, while "–" denotes areas that are specifically identified as not changing.

more a function of technological and data-analytical techniques rather than the patterns of change in rCBF.

Changes engendered by reading have also been used to investigate language production. In the functional neuroimaging literature, reading aloud is typically conceptualized as the visually-mediated analog of repetition. In their SPET study, Ingvar and Schwartz (1974) had their subjects "read aloud from simple texts from an ordinary weekend magazine" and then compared the resulting rCBF pattern to a blindfolded resting control state. Again, there were no significant changes in mean hemispheric flow between the two conditions. However, regional increases were noted in premotor, sensorimotor, superior sylvian, middle temporal, and temporo-parieto-occipital regions. The increase in the temporo-parieto-occipital activity was greater than the increase seen when comparing the automatic speech task to the resting control state. Petersen and coworkers (1989) included a vocal single word reading task in their paradigm, and they compared the resulting rCBF pattern to the pattern seen during silent reading of single words. Results suggested that vocalization increased activity bilaterally in the primary sensorimotor mouth region, SMA, superior anterior cerebellum, and superior colliculus. Unilateral increases were seen in the left inferior premotor cortex, left rolandic/sylvian junction, and right mid-sylvian superior temporal region. Of these increases, the sensorimotor mouth, cerebellar, and collicular increases were greatest.

Two functional neuroimaging studies have been performed to examine the pattern of rCBF engendered by repetition of aurally presented words. Petersen and colleagues (1989) required subjects to repeat aurally presented nouns. When subtracting the pattern of blood flow during passive listening to single words from the pattern seen during repetition, the authors reported bilateral increases in the sensorimotor mouth region and SMA and unilateral increases at the left rolandic/sylvian junction, in left inferior premotor cortex, and in right mid-sylvian superior temporal cortex. Of these increases, the largest changes were the bilateral sensorimotor and right superior temporal changes. In contrast, Wise and colleagues (1991) had subjects perform a repetition task aimed specifically at localizing regions involved in the processing of novel lexical-semantic information. In the stimulation task, subjects were required to repeat single aurally-presented concrete and abstract nouns. In the control task, subjects

were required to say the same word when aurally presented with reversed words. Comparison of these two patterns of activation suggested that there was significantly greater activity in the left posterior superior temporal region during the repetition of concrete and abstract nouns than during the control task.

Petersen and colleagues (1989) note that previous work from their lab suggests that a number of the increases seen during reading aloud and repetition may have more to do with motor programming in general than with single word processing *per se*. For instance, previous studies have shown very similar activations in left inferior premotor and left inferior sensorimotor cortex in simple tongue movement and hand movement (Fox, Pardo, Petersen, & Raichle, 1987). Similarly, rCBF in SMA has been shown to increase during simple tongue, eye and hand movement (Fox et al., 1987; Fox, Fox, Raichle, & Burde, 1985). In addition, Fox, Raichle, and Thach (1985) reported that superior, anterior cerebellum and colliculas have been shown to increase in terms of rCBF during hand and eye movements. The authors account for the lack of activation of the latter structures in the repetition of aurally presented words by reporting that these structures (at least the cerebellar areas) did, in fact, increase in flow, but not to a statistically significant extent.

A summary of the findings related to vocal reading and repetition is contained in Table 2-4. When comparing these findings to those noted in the investigations of automatic language as well as to the motor findings of the St. Louis lab, it is apparent that the majority of changes during these tasks appear to be related to the initiation and execution of speech rather than language programming *per se*. Exceptions are seen when comparing reading and repetition to control tasks in which there was little or no language stimulation (Ingvar & Schwartz, 1974; Wise et al., 1991). Both of these groups noted increases in left posterior superior temporal cortex. It is impossible to differentiate receptive from expressive demands in these two comparisons, however. Another exception which appears to be language-related is the consistent activation found in Broca's area.

The task which has been used the most frequently in exploring language production with functional neuroimaging is single word generation. This has been done using a number of different formats. The format requiring the least generativity to a single stimulus is that used by Petersen and

Table 2-4

Summary of Functional Neuroimaging Studies on Story, Reading Aloud and Repetition

Study	Stimulation Task	Control Task	Frontal Operculum	Dorsolateral Prefrontal	Inferior Lateral Prefrontal	Medial Superior Frontal (SMA)	Posterior Superior Temporal	Inferior Parieto-Occipital	Other
Haxby & Schouten (1974) ONLY 1 LEFT HEMISPHERE STUDIES	Hear aloud from magazine article	Restate silently with eyes closed	L	-	-	-	-	L	L Middle Temporal
Horwitz et al. (1998)	Read single words aloud (visual stimuli)	Passively read single words	L	-	-	B	-	-	B Extrastriate Fusi, B Superior Anterior Cerebellum, B Cerebellum L Rolandic Sylvian pariens R Mid-superior Temporal
	Repeat single words aloud (auditory stimuli)	Passively listen to single words	L	-	-	B	-	-	B Rolandic/inter Fusi L Rolandic/ Sylvian pariens R Mid-superior Temporal
Wise et al. (1991)	Repeat concrete and abstract nouns	Say the same word each time a reviewed word is heard (only reviewed words presented)						L	

Note: B denotes bilateral change in activity, L denotes change in left hemisphere, R denotes change in right hemisphere, M denotes change in a midline region. Empty cells denote those that are not discussed, while "-" denotes areas that are not specifically identified as not changing.

colleagues (1989). The basic format is the same as described previously, in that subjects are presented with high frequency English nouns at the rate of 1 Hz. In the verb generation task, subjects are instructed to generate a verb associated with each noun. This task was presented with both visual and aural stimuli. When the pattern of rCBF observed during vocal reading was subtracted from the pattern engendered by verb generation (visual stimuli), increased activity was noted in anterior cingulate cortex (two foci, one inferior to the other), left prefrontal cortex (inferior, lateral, and dorsolateral; roughly areas 44-47), and throughout the cerebellum (bilateral posterior, right inferior lateral, and anterior cerebellum/colliculus). Anecdotal report also suggests that a bilateral decrease was seen in "sylvian-insular cortex" (Raichle, 1991). When the pattern of rCBF observed during repetition was subtracted from the pattern engendered by verb generation (aural stimuli), activation was noted in the anterior cingulate regions, left inferior frontal cortex, right inferior lateral cerebellum, and anterior cerebellum/colliculus. It is unclear whether the presence of the aforementioned bilateral decrease in sylvian-insular activity occurs in both versions of the verb generation task.

In addition to the previously discussed limitations which apply to the studies of Petersen and colleagues, another complication arises in comparing the verb generation condition to the vocal reading/repetition tasks. Although the structure of the verb generation condition minimizes the amount of generativity associated with one stimulus and maintains consistency in presentation rate between it and the other Petersen et al. tasks, behavioral data suggest that the task is much more demanding than the others. The authors anecdotally report that the subjects reported this task to be the most difficult (Petersen et al., 1989), and Fox (as cited in Raichle, 1991) claimed that verbs were successfully generated to only 40% of the nouns on average. Thus, both rate of language output and relative effort may be having some systematic impact unaccounted for by the design of the tasks. Studies examining the effects of task difficulty upon rCBF suggest that such variation may lead to systematic differences in prefrontal flow indices, with more difficult tasks leading to greater rCBF increases in this region than easier tasks (Gur et al., 1988). Indeed, recent anecdotally-reported findings suggest that when the presentation rate is changed from 1 Hz to 1.5 Hz, one observes a marked difference in the resulting subtraction image (Raichle, 1991). For instance, one observes a dramatic increase in the activity of the

left posterior superior temporal region. Raichle notes that this response was present in the 1989 study, but its magnitude did not reach statistical significance. Unfortunately, the effect of this manipulation on the activity observed in other regions is not discussed.

Other studies carried out in the St. Louis lab described by Raichle (1991) have examined the effects of practice on the observed rCBF responses during the tasks. He reported that, with as few as six practice trials with the same word list, one sees a significant reduction in the magnitude of the rCBF response in left prefrontal cortex, anterior cingulate cortex, left posterior temporal cortex, and the right cerebellar hemisphere. Further neuroanatomical specification was not provided. Accompanying these reductions was a significant *increase* in sylvian-insular activation bilaterally. It may be more accurate to view this latter increase as a recovery from the initial decrease seen in the early trials, however, as the activity level in the sylvian-insular area after practice is back to levels observed during "normal speech" rather than above its "baseline language production" level. Raichle likens the distribution of rCBF seen in practiced verb generation task to that observed during the reading of nouns aloud. It should be emphasized that the findings concerning presentation rate and practice are impossible to evaluate fully since the results and methods employed in arriving at the conclusions have never been formally reported. Thus, one is left to accept the findings "on faith," and any further hypotheses based upon this work must be made with the utmost caution.

Another format of word generation has been used by Wise and his colleagues (1991). These investigators had subjects silently generate as many verbs associated with an aurally-presented noun as they could within four seconds. Subjects were instructed to signal their arrival at the first verb by opposing thumb and forefinger of the left hand, and they were asked to limit themselves to thinking of verbs without forming sentences. Fifteen nouns were presented per minute, and subjects retrospectively reported an average of two to four generated verbs per noun. When comparing this scan to the one acquired during the resting control state, the authors noted increased activity in the left posterior superior temporal gyrus, left posterior middle frontal gyrus, and midline SMA. Notably, the activity level reported for posterior superior temporal cortex during the verbal generation task did not

vary from that reported during listening to nonwords of typical English phonological structure or deciding if two words are correctly categorized semantically.

Single word generation has been investigated with a different methodology by another group of investigators at Hammersmith. Friston, Frith, Liddle, & Frackowiak (1991a) had four subjects (1) count out loud, (2) decide if aurally-presented morphemes were real words ("correct" or "incorrect"), (3) generate animal names, (4) generate words that start with the letter "a." Two resting control tasks during which the subjects were instructed to recline quietly with eyes closed were not used in comparisons. As pilot work showed that the average rate of output in tasks 5 and 6 was approximately one word every 2.5 seconds during the first 90 seconds of the task, this rate was chosen for the counting and lexical decision tasks. In the lexical decision task, high frequency concrete words beginning with the letter "L" were used, with half of the stimuli being orthographically regular nonwords in which the first letter of a word was replaced by "L."

For the purposes of their analysis, the authors combined the images from the word generation conditions into an "average word generation" image. No explanation for this combination was offered, and no direct comparison of the two generation tasks was reported. The SPM's derived by comparing the generation image to the counting image and the lexical decision image to the counting image, respectively, were not displayed in the report. The authors noted that the only region to decrease significantly in the generation tasks and increase significantly in the lexical decision tasks was left posterior superior temporal cortex. Comparison of the pattern of rCBF in the average word generation image to that seen in the lexical decision task suggested greater rCBF bilaterally in the anterior cingulate and unilaterally in left dorsolateral prefrontal cortex (Brodmann's areas 9, 46), left parahippocampal gyrus (area 28), and left parietal cortex (supramarginal gyrus) during the generation conditions. During the lexical decision task, on the other hand, greater activity was seen bilaterally along the superior temporal gyrus and unilaterally in the right frontal operculum.

In addition to the changes in level of activity, Friston and coworkers also explored the correlation between the average left dorsolateral prefrontal activity and all other regions across scanning conditions. They noted significant negative correlations between left dorsolateral prefrontal

and superior temporal regions. Although the authors do not discriminate between superior temporal regions when describing this negative correlation, examination of the figures suggests a substantial asymmetry. On the right side, the negative correlation appears to encompass the entire superior temporal region, with extension into inferior parietal and occipito-temporal cortices. In the left hemisphere, however, the negative correlation appears to be limited to more anterior superior temporal regions (perhaps primary auditory cortices), with much less involvement of posterior superior temporal cortex or nearby association areas. Unfortunately, significant positive correlations were not addressed in the report.

This same group of investigators reportedly explored single word generation again with a methodology virtually identical to their other study (Frith, Friston, Liddle, & Frackowiak, 1991). The authors reported that in this investigation, the word generation task was to generate as many jobs as one can think of rather than animal names. The primary differences between the two studies reportedly lie in the manner in which the data were analyzed. In this study, Frith and coworkers converted radioactive counts to rCBF equivalents following the algorithm described by Mintun, Fox, and Raichle (1989). Analyses suggested that global blood flow decreased in all activation tasks relative to the resting control state. In contrast, there was no difference in global blood flow between cognitive activation tasks.

Statistical parametric maps (SPM's) were also computed to determine regional changes. In order to identify the neural substrates important to the generation of single words, the investigators compared the mean of the images acquired during both word generation conditions to the mean of the images acquired during rest, counting, and lexical decision tasks. Interestingly, the SPM's displayed for this comparison appear identical to the ones displayed by Friston and colleagues (1991a) in their comparison on the average word generation image to the lexical decision image, thus suggesting increases and decreases in rCBF in exactly the same locations. In order to identify the neural substrates important to lexical decision, the pattern of rCBF engendered by the lexical decision task was compared to the mean pattern of the other tasks. Bilateral increases were noted in "periauditory" and superior temporal regions, while unilateral increases were seen right inferior prefrontal cortex and

in the left frontal pole. Bilateral decreases were seen in the posterior cingulate gyrus. In order to investigate the covariance of activation between regions, correlations were computed between the pixel in the left dorsolateral region with the most significant t-statistic in the generation vs. others comparison and all other pixels. The displayed SPM was again identical to the one displayed by Friston and colleagues exploring their analogous correlation, suggesting negative correlations in the same locations. Positive correlations were not reported.

The investigations conducted by Frith, Friston, and their colleagues have much in common. Methodologically, they both use the previously-described image construction and data analysis algorithms defined by Friston and colleagues (1989, 1990, 1991b). They also both relate their hypotheses to an explicitly-defined, mathematically-derived model. In addition, the authors investigated not only absolute differences in activity, but also correlations between regions in an attempt to understand the covariance of activity between regions during specific tasks. However, a number of factors cloud the interpretation of the studies. At the level of data analysis, the combination of images acquired during different stimulation tasks into a mean image designed to reflect a specific cognitive process is overly simplistic and confounds the interpretation of any comparison with this mean image. Likewise, the use of a single pixel as the "representative" of the activity of a given region of cortex makes one extremely susceptible to outliers, even with the "smoothing" of the images discussed earlier. Conceptually, a major confound in drawing conclusions about the role of the superior temporal gyrus is the fact that the amount of information aurally presented was not held constant across conditions. Given that the greatest increase in activity in the superior temporal region was seen in the lexical decision task, which provided the most aural stimulation, it is difficult to separate this factor out from the contribution of cognitive processes. In addition, the rates of output, although relatively consistent over the first 90 seconds of each stimulation task, were different in nature. The lexical decision and counting tasks each involved a constant output demand, while the word generation tasks involved a much less linear output function. Thus, one wonders if one is looking at as homogeneous a cognitive process over the scanning interval in the word generation tasks as in the lexical decision task. Also, the lack of a comparison between generativity tasks is not

discussed. This is puzzling, as these tasks reflect somewhat different processes. In addition to subtly different cognitive requirements, these two tasks have been shown to differ in terms of level of performance (Lezak, 1983). Some sort of ratings of the relative difficulty of each task also would have been helpful, as this may play an important role in determining extent and/or magnitude of activation, especially in prefrontal regions (Gur et al., 1988). Finally, the exact duplication of results on a very small sample suggests that these results are separate reports of the same investigation rather than a replication, although it should be noted that Frith and colleagues do not present their data as replicatory.

Warkentin, Risberg, Nilsson, Karlson, and Graae (1991) investigated single word generation in a more traditional format. These authors used ^{133}Xe inhalation SPET in 39 subjects (19 men, 20 women) to examine rCBF patterns during a resting control state and while generating as many words as possible that begin with a given letter for sixty seconds. Regional analyses within tasks showed greater rCBF in frontal than in post-central or temporal regions, a finding consistent with earlier studies (Ingvar & Schwartz, 1974). Comparison of the two rCBF patterns suggested that there were no differences in mean hemispheric flow within or across conditions. Regionally, however, word generation was noted to engender a significant increase in flow in the left anterior frontal region, while flow was decreased in left superior sensorimotor and left anterior parietal/sensory regions. In temporal and frontotemporal regions, right-sided values were greater in absolute terms and increased more than did left-sided values during single word generation. When the investigators combined the values for the three most anterior frontal probes into a single mean, they found that, during word generation, the flow values from the left prefrontal region were significantly higher than the values of their contralateral homologues. In addition, the left prefrontal mean was higher during the word generation task than at rest. In contrast, there was no difference in the right prefrontal mean across tasks. Although females' mean hemispheric flow was slightly higher than that of their male counterparts, there was no difference in prefrontal rCBF change according to gender. Likewise, the prefrontal flow values observed in sixteen "highly productive" subjects did not differ from those of the rest of the sample.

The investigators went on to discuss some of the individual variability in their data. They reported that six subjects (15% of their sample) showed neither left nor right increases in prefrontal flow values during the word generation task. As analyses showed that this group's resting prefrontal values were significantly higher than those of the other subjects, the authors hypothesized that the change was indeed present but masked by the already high baseline level of activity. The authors do not speculate upon how this dynamic would work, however. This hypothesis assumes one of two possibilities. First, it may be that there is a maximal value for rCBF in the left prefrontal cortex, thus preventing the high baseline group from showing enough of a difference to reach statistical significance. On the other hand, it may be that there are areas in prefrontal cortex whose flow values are not affected by word generation, and these areas were already activated to such an extent in the resting condition that the increase in flow secondary to word generation did not constitute a statistically significant increase in flow to the region.

There are a number of strengths to this study. Foremost is the nature of the sample. Sample sizes under 15 are the norm for this literature, and samples are commonly made up of either inpatients or groups of normals whose members may be familiar with the hypotheses or stimuli used in the study. Neither of these weaknesses are present in this study, as all 39 subjects were recruited through local advertisement. While this undoubtedly did not result in a sample representative of the population at large, it is certainly intuitively more comfortable to make generalizations based on a large sample of experimentally-naive subjects. In addition, these subjects were screened in order to rule out mental illness, substance abuse, hypertension, and neurological disorders. Finally, a brief neuropsychological battery was administered to insure that subjects were within normal limits in terms of verbal ability, verbal memory, spatial ability, reaction time, and visual constructive ability (although details and scores of tests were not reported).

Clear interpretation of the data is clouded, however, by a lack of control conditions. Since the cognitive resting state as defined by Warkentin et al, is inherently uncontrolled, it is impossible to attribute the observed rCBF changes to a specific cognitive act; indeed, the uncontrolled nature of the resting condition may explain in part some of the variability in the observed changes. Again, as with

other SPET studies, the poor localization abilities of the technique must be kept in mind when interpreting the results. This limitation tempers the power of the left-prefrontal activation finding in particular, as the authors had to combine three relatively poorly-localized regions (with an unknown subcortical component) before their findings became significant. As the resulting comparisons involve large regions of both lateral and medial cortex, it is difficult to know exactly what the results mean.

A summary of the findings related to single word generation may be found in Table 2-5. As with the investigations of other components of language, there is substantial variability between labs. There are a number of consistencies, however, in examining those regions which appear to become increasingly activated by the generation of single words. The most consistent increases in rCBF are found in the anterior cingulate and in the left dorsolateral prefrontal cortex. Given the extensive interconnections between these regions as well as their theorized role in systems which mediate intention (Heilman, Watson, & Valenstein, 1985), these activations are not surprising. Most other findings are consistent within but not across laboratories. As most experimental and data-analytic parameters vary considerably from laboratory to laboratory, this variability is also not surprising. Substantially different findings are even found within groups (Friston et al., 1991a; Frith et al., 1991; Wise et al., 1991). In comparing studies, it is again evident that the factors of rate of stimuli presentation and generation are extremely important to determining one's results and subsequent interpretation of the neural instantiation of networks required to generate single words.

A concrete example of this point is provided by the comparison of the findings reported by the Hammersmith group. The results reported by Friston, Frith, and colleagues' word/animal/job generation tasks appear to be at odds with those of Wise and colleagues (1991). Wise and colleagues find that both left dorsolateral prefrontal cortex and left posterior superior temporal cortex become significantly activated in a verb generation task, while Friston, Frith, and colleagues report a decrease in left superior temporal activity and an increase in left dorsolateral prefrontal activity during word generation. There were subtle differences in the tasks which may account for the differences. Friston et al./Frith et al. (1991) had their subjects generating animal names or words that begin with the letter

Table 2-5.
Summary of Functional Neuroimaging Findings during Word Generation

Study	Stimulation Task	Control Task	Frontal Operculum	Dorsolateral Prefrontal	Inferior Lateral Prefrontal	Medial Superior Frontal (SMA)	Posterior Superior Temporal	Temporo-Parieto-Occipital	Other
Petersen et al. (1989)	Generate associated verbs (visual/aural)	Read single visual word aloud	L		L	M		—	**R** Anterior Cingulate (two foci) **M** ? **B** Prefrontal Cerebellum **R** Cerebellum Lateral Cerebellum (**B** Superior is 'fixation' target)
	Generate associated verbs (semi-overt)	Repeat single noun	L		L	M		—	**M** Anterior Cingulate (two foci) **M** ? **R** Cerebellum Lateral Cerebellum (**B** Superior is 'fixation' target)
Wise et al. (1991)	Generate verbs	Recite silently with eyes closed	L		L	**R** (decrease)	L		**R** Anterior Cingulate **L** Parietal ? Posterior Cyrus **B** Inferior Superior Temporal Gyrus
Frith et al. (1991)	Average of generation to 'A' and generation of any name	Average of reciting silently with eyes closed, counting aloud, and reciting months to 'A' and generation of any name		**R** (decrease)	L	M	**R**	B	**R** Anterior Cingulate **L** Parietal ? Posterior Cyrus **B** Inferior Superior Temporal Gyrus
	Average of generation to 'A' and generation of any name	Lexical decision		**R** (decrease)	L	M	**R**	B	**R** Anterior Cingulate **L** Parietal ? Posterior Cyrus
Warburton et al. (1996)	Generate verbs to a single noun presented or retrieve names	Recite silently with eyes closed			L			L	**B** Anterior Cingulate **L** Parietal ? Posterior Cyrus

Note. R denotes bilateral change in activity; L denotes change in left hemisphere, R denotes change in right hemisphere, M denotes change in a midline region. Empty cells denote those that are not discussed, while "—" denotes areas that are not specifically identified as not changing.

'a' or jobs for a minimum of 90 seconds, while Wise et al. (1991) had their subjects generating "appropriate verbs" to concrete nouns which were presented at a rate of one every four seconds. In addition, Wise et al's subjects retrospectively recalled producing 2-4 verbs every four seconds, while three out of four of Friston et al's subjects generated words at a rate of approximately 2 words every five seconds (the fourth subject was slower). Thus, in comparison to verb generation, the generation task of Friston, Frith, and colleagues was a) less restrained semantically, b) less demanding in terms of output rate, and c) more exhaustive in terms of the required amount of "searching" (lexical or semantic, respectively).

In addition, it is important to keep in mind the choice of control tasks made by each group of investigators. Friston et al. compared his "average word generation" images to images acquired during "automatic language" (i.e. counting aloud), while Wise et al. utilized an unstimulated rest condition as his control. Thus, the former comparison theoretically represents those areas that become activated primarily as a novel word generation resulting from lexical and semantic searches, whereas the latter would encompass all language functions involved in silently generating verbs to nouns. One might thereby conclude that the activation of posterior superior temporal cortex is important in the generation of words at a cognitive level "lower" than the "search" function *per se*. If this is the case, then one must presume that Friston's automatic speech task activated left posterior superior temporal cortex to such an extent that word generation did not add significantly to this level of activation. Such a presumption is consistent with the findings of Ingvar & Schwartz (1974) and Larsen et al. (1978), both of whom showed left posterior superior temporal cortex activation (although not in as well-defined a manner as did the PET studies) during "automatic speech" tasks as compared to rest control conditions.

Finally, a difference discussed solely in the context of interpreting Friston et al.'s findings may be critically important: that is, the fact that Wise et al.'s subjects were being aurally presented with new information every four seconds, while Friston et al's subjects were being presented with none. If left posterior superior temporal cortex is involved in the "decoding" of incoming linguistic information, then this discrepancy alone would account for both a) Friston et al's differences between lexical decision and word generation (between which there was also a great discrepancy in the rate of stimuli

presentation), and b) the differences between Friston et al's word generation findings and Wise et al's findings. One might point to the lack of posterior superior temporal cortex response in the Petersen et al. (1989) verb generation task, in which subjects were presented with new information (either visually or aurally) at a rate of 1 Hz, as confusing in light of this interpretation. However, the "activation" engendered by this task was reported in the context of a (verb generation) – (repetition) subtraction image, thus theoretically "removing" the activation engendered by the rate of presentation of stimuli *per se*.

The final component which has been examined in functional neuroimaging studies is the construction of discourse. Although this represents an extremely complex combination of cognitive components, it is the only data to date which are able to even indirectly examine the instantiation of grammatical formulation. Lechevalier, Petit, Eustache, Lambert, Chapon, and Viader (1989) used ^{133}Xe inhalation SPET to examine language formulation in seven men and three women on their Neurology unit. Images were acquired for a resting control state, during which subjects were instructed to neither move nor speak for ten minutes, and during a word definition task, during which subjects were instructed to "say as much as they could" about a list of 17 nouns and 8 transitive verbs of high frequency by either providing a definition of the word or using it in an appropriate context. A new word was presented every 30 seconds. When comparing the patterns of rCBF from these two conditions, the authors found significant bilateral increases in hemispheric flow (approximately 16% on the right and 15% on the left). Regionally, increases were noted in virtually every part of cortex, with the greatest increases noted bilaterally in the inferior parietal cortex, right superior parietal cortex, right dorsolateral frontal cortex, left posterior superior frontal, and left inferior frontal cortices (approximately Broca's area). The location of the left posterior superior frontal activation suggests involvement of SMA, but this was not investigated further. In addition, the study was subject to the previously-discussed limitations of the ^{133}Xe inhalation SPET technique.

Finally, Wallesch, Henriksen, Kornhuber, and Paulson (1985) had six staff members of the Department of Neurology and the Language Pathology Unit of Ulm University perform a number of tasks: (a) rest, (b) oral movements without phonation, (c) repeated counting from one to twelve, (d)

production of "random" consonant-vowel and consonant-vowel-consonant syllables, (e) retelling of a magazine story read ten minutes before starting, and (f) silent retelling of a story as in (e) without any detectable coarticulation. Subjects were instructed to speak (silently in condition f) at a rate of 1 syllable per second. Analyses were all performed using a 2 cm thick transverse image containing Broca's and Wernicke's areas, head of the caudate, lenticular nucleus, and the thalamus. The slices used in the comparisons were constructed by creating normalized flow distribution images of the slice (rCBF over gCBF for each pixel) for each subject, averaging these normalized images across subjects within each condition after "careful positioning to minimize the effect of different size and shape of the heads," and comparing the averaged task images to each other with a subtraction algorithm. The average amount of change across all pixels between the tasks being compared was then calculated, and "activated regions" were those pixels in which change was one or two standard deviations greater than average.

When subtracting the rest condition from the vocal storytelling condition, the authors identified bilateral increases in posterior temporal/inferior parietal/anterior occipital regions (the uncertain angle of the cut makes it difficult to determine precisely the location, and it is referred to by the authors as "retrorolandic") and unilateral increases in left frontal operculum, right lenticular nuclei, left head of the caudate nucleus, medial anterior frontal region (possibly anterior cingulate), left anterior temporal regions, and in the left anterior thalamic/pallidal region. Subtraction of the rest image from the silent storytelling image revealed bilateral increases in the same "retrorolandic" regions, in the head of the caudate nucleus, and throughout the frontotemporal cortex, while unilateral increases were seen in left posterior thalamic regions. When subtracting the rCBF pattern engendered by syllable generation from that engendered by vocal storytelling, the authors noted bilateral increases in similar "retrorolandic" regions and unilateral changes in left Broca's area, left head of caudate, left anterior thalamic region, and anterior cingulate. A weaker increase was seen in a more widespread fashion over the left frontal lobe (both laterally and medially) and in the right head of the caudate. Subtraction of the counting image from the vocal storytelling image revealed bilateral increases in the same "retrorolandic" regions and the head of the caudate, while unilateral increases were seen in left

frontal operculum, left anterior medial frontal cortex (anterior cingulate), left anterior frontotemporal regions, right anterior medial frontal regions (anterior cingulate), and left anterior thalamus.

There were a number of technological and analysis issues which cloud the interpretation of this data. Foremost is the manner in which regional flow distributions were compared between conditions. In constructing "average flow distribution" scans, the authors necessarily limit the accuracy of their localization of brain areas due to the superimposition of different brains upon each other with no attempt at standardization. This, combined with the relatively thick SPECT and CT slices and poor resolution of the technique available at that time restrict interpretation to "general area" statements at best. This difficulty in interpretation is compounded by a lack of presentation of the rCBF data in numerical form, thus forcing the reader to rely upon the investigators drawings of the regions of activation as the only measure of extent of activation of the various regions. This makes direct comparison between regions very difficult. Furthermore, in comparing slices, decreases in flow were not mentioned: it is unclear whether this is due to their absence or the investigators' emphasis on increases.

The investigators' method of using the standard deviation of change in the ratio of rCBF to mean CBF as a measure of significance also has ramifications which should be kept in mind, especially in light of their lack of mention of decreases in activity. If most regions of the brain respond to a task in a relatively consistent manner, then the standard deviation of change will be small, and it will take less deviation from the mean of change to be considered significant. In contrast, if there is more variability (in both positive and negative directions) in the degree of change across regions of the brain, then a substantially greater change may be required to reach statistical significance.

Conceptually, this study had some limitations as well. Output in each condition was limited to one syllable per second, thereby necessitating each subject's monitoring of rate of output. Aside from the fact that this sort of monitoring is not usually associated with the language phenomena to which the results were to be generalized, it is uncertain whether the effort needed to maintain this rate of output would be consistent across the varying tasks, given their disparate nature (single word or syllable output vs. narrative language). In addition, only those comparisons between high levels of the

hierarchy (story retelling) and lower levels of the hierarchy (rest, syllables, counting) were discussed. One is left wondering whether the comparisons between more adjacent steps simply were not performed, or if statistically significant differences were observable only between more distant steps.

The results of the investigations of discourse are summarized in Table 2-6. The most obvious characteristic of these data is their variability. As the demands of these tasks are the most complex and the designs of the comparisons to be made were among the most uncontrolled, this is not surprising. Perhaps the most accurate statement that can be based on these data is that the production of discourse engenders wide-spread activation both cortically and subcortically when compared to relatively basic linguistic tasks. The involvement of left frontal operculum, anterior cingulate cortex, and left head of the caudate nucleus appear to be the most consistent findings across comparisons, but delineation of which specific linguistic functions these changes may be involved in is simply impossible based on the available discourse data.

As with single word comprehension, an integration of the functional neuroimaging and lesion data concerning the production of language yields a number of consistencies as well as unanswered questions. It is clear that the anterior cingulate, left frontal dorsolateral/opercular (Brodmann's areas 44-46) are somehow involved in the normal production of language, as these regions are consistently shown to increase in rCBF when comparing a language production task to rest. The anterior cingulate activation appears to be most strongly related to the drive to generate language, while the dorsolateral frontal cortex and frontal operculum appear to be influenced by issues of intention as well as language formulation. It is unclear at this point exactly how the frontal opercular activation seen in normals is to be reconciled with the finding that lesions confined to this area usually have minimal impact on language function (Mohr et al., 1978; Nadeau, 1988); nevertheless, the consistency of the finding suggests that this region is involved in the normal production of language in some fashion. Finally, it is apparent by examining the available data that no functional neuroimaging studies have been done which adequately address the grammatical formulation during the production of language.

Table 2-6.
Summary of Function and Neuroanatomy Findings During Discourse Production.

Study	Stimulation Task	Control Task	Frontal Operculum	Dorsolateral Prefrontal	Inferior Lateral Prefrontal	Medial Superior Frontal (SMA)	Posterior Superior Temporal	Temporo-Parieto-Occipital	Other
Schlosser et al. (1998)	Define (or rate a given word) for 30 seconds	Rest	L	R	L	M	B		Most regions other than inferior temporal and superior parieto-occipital. L Insula; R Hemispheres
Warburton et al. (1996)	Vocally retell a magazine story read 10 minutes earlier	Rest	L			M	B		M Anterior Cingulate; L Anterior; L Head of Caudate; L Anterior Thalamus; L Putamen; L Thalamus
	Specify retell a magazine story read 10 minutes earlier	Rest	B			M	B		M Insula-like Nuclei; L Anterior Cingulate; L Posterior; L Thalamus
	Generate indeed nonsense syllables	Generate indeed nonsense syllables	L			M	B		M Anterior Cingulate; L Head of Caudate; L Anterior; L Thalamus
	Counting repeatedly from 1 to 12	Counting repeatedly from 1 to 12	L			M	B		
	Vocally retell a magazine story read 10 minutes earlier		B			M	B		B Head of Caudate; L Anterior; B Anterior Thalamus; L Anterior Ventro-temporal regions

Note. B denotes bilateral change in activity, L denotes change in left hemisphere, R denotes change in right hemisphere, M denotes change in a midline region. Empty cells denote those that are not mentioned, while shaded cells denote areas that are specifically identified as not changing.

It appears that a phenomenon analogous to that seen in the investigations of single word comprehension occurs when investigating language production: that is, that one must control for the "primary responses" before being able to elucidate the region involved in the "higher" processes of language formulation. In the case of language production, these "primary" responses appear to be the basic initiation and motor execution of a language response. It may well be the case that the anterior cingulate, SMA, and dorsolateral frontal responses are strongly related to these processes, and that these processes are so fundamental to the production of language that they in turn are represented by the largest rCBF response (analogous to the primary sensory responses and comprehension). Thus, in order to investigate the processes of message formulation, labeling of the message via the output lexicon, further defining the message through concatenation and syntactic manipulation, and phonological programming of the message, one must do so in the context of a paradigm in which both primary sensory and output processes are controlled as much as possible.

In summary, then, there are a number of questions which remain unanswered in the comprehension of single words and the generation of language. Although lesion studies have been extremely informative about potential sites of specific linguistic functions, one is always limited by the inability to ascertain whether one is observing the function of an impaired system, an intact compensatory system, or some combination of the two. The study of normals using functional neuroimaging is meant to address these ambiguities, but to date these investigations have been marked by experimental paradigms that make it extremely difficult to delineate the occurrence of specific cognitive processes and how these processes might relate to the patterns of functional activity that are reported. Likewise, it seems that no two laboratories share the same equipment or data analysis algorithms, and the extent to which each reported set of data actually reflects the biological data that it is meant to reflect may vary widely. As such, the replicability of results becomes of the utmost importance.

There are precious few results that have been replicated across a number of investigations, and most of these are consistent with what one would predict based on the lesion literature. The responses of primary and secondary sensory cortices are consistently shown according to expectations. Likewise,

posterior area 37/anterior area 19 appear to be consistently involved in the early stages of the comprehension of the written word, while the left posterior superior temporal region/temporo-parietal junction (Wernicke's area, inferior supramarginal gyrus, area 37) is consistently identified in the comprehension of the spoken word. During the production of language, one almost always sees increased activity in the anterior cingulate, supplementary motor area, left dorsolateral frontal cortices, and left frontal operculum.

There are a number of contradictory findings and questions which have yet to be carefully investigated, however. There are no interpretable data available on the functional neuroimaging of grammatical formulation in language. Likewise, the roles of the different regions represented in the temporoparietal junction have yet to carefully investigated in tasks that were matched according to input and output demands as well as difficulty level. In addition, the apparently-contradictory findings about the roles of the inferior lateral prefrontal cortex (area 45 and/or 47) and posterior superior temporal region in the semantic comprehension of language remain confounded with stimulus modality and poor choice of disambiguating control conditions. Furthermore, the impact of task difficulty on reports of changes in prefrontal activity have never been systematically examined in this literature. Since these regions are certainly important to the production of single words and quite possibly to syntactic function as well, this sort of statistical control is extremely important.

The purpose of the current study, then, is to address a number of these issues in the context of a regional cerebral blood flow study of word generation. Tasks were designed to preferentially assess the phonological, semantic, and syntactic aspects of language formulation. In order to control for the "primary" responses involved in comprehension, subjects were presented with a constant number of stimuli at a constant rate across tasks. Similarly, "primary" output responses were controlled by requiring the subject to formulate a response in each task which was preferentially geared towards the targeted linguistic function (i.e. phonological formulation, semantic formulation, syntactic formulation). Also, language formulation occurred in the absence of vocalization in an attempt to control activation related to motor execution of the response. Finally, tasks were relatively equated on the dimensions of input demand, output demand, and difficulty.

Hypotheses

Across-task Predictions:

(a) There will be no systematic effect of type of generative task (phonological, semantic, or syntactic) on global blood flow. This hypothesis is based on the fact that, to date, when comparing between "linguistically activated" states, differences in global blood flow have never been shown.

(b) Regions of interest on the right side of the brain will not change across tasks. Although research exists implicating simple semantic functioning in the right hemisphere, this processing does not appear to be relatively localized as it is on the left (Baynes, 1990).

(c) The activity seen in the left posterior superior temporal region (Wernicke's area) will be significantly greater in the semantic and syntactic tasks than it will be during the phonology task. This hypothesis is based on the apparent specialization of this region for lexico-semantic processing indicated in both classical aphasiology and an integration of the available functional neuroimaging data.

(d) The activity seen in left dorsolateral prefrontal cortex (Brodmann's areas 9, 45-46) will be significantly greater in the syntactic task than in the other two tasks. This hypothesis is based on the work on agrammatism as well as other frontal lobe lesions which indicate that syntactic processing (particularly at the sentence level) is handled preferentially by left prefrontal regions (Alexander, Benson, & Stuss, 1989; Goodglass & Menn, 1985; Nadeau, 1988). As the demands for novel output are to be held relatively constant across tasks, greater activity in this region in the syntax task should be indicative of syntactic processing rather than verbal generation *per se*.

(e) The activity of regions theoretically implicated in language processing will be significantly correlated across tasks, reflecting the change in activity of an integrated network.

<u>Within-task Predictions</u>

(a) Each condition will be marked by an asymmetry of flow in dorsolateral prefrontal cortex. This hypothesis is based on the consistency with which these results are found in the imaging literature as well as the impediment in verbal fluency which is seen in lesions of left prefrontal, but not right prefrontal, dorsolateral prefrontal regions. As this consistency holds in the literature regardless of vocal or nonvocal language generation, it is likely to be present in all three of the experimental conditions.

(b) The semantic and syntactic tasks will be marked by significant asymmetry in Wernicke's area due to the lexico-semantic processing demanded by these tasks. This hypothesis is based on the same foundations as across-task hypotheses (b) and (c) above.

CHAPTER III

METHODOLOGY

<u>PILOT STUDY #1</u>

The purpose of Pilot Study #1 was to determine the relative difficulty levels of the three tasks to be used in the primary study. These tasks are as follows:

Nonword rhyming – the subject is presented five nonwords conforming to the spelling rules of the English language and is asked to produce a rhyming nonword for each stimulus;

Semantic association – the subject is presented with five words and is asked to generate a semantic associate for each one. Word sets consist of *either* five nouns or five verbs in an effort to make implicit syntactic generation less likely;

Syntactic generation – the subject is given five words specifying a) sentence structure (either passive or cleft-object), b) statement or question format, c) subject, d) verb, and e) object, and is asked to generate an appropriate sentence. The sentence structure and format is always presented in the top and second-from-top positions, respectively, while the order of the subject, verb, and object is randomized across stimuli sets.

Specific issues to be examined in pilot study #1 were the patterns of error and time taken to respond to each stimulus. In an attempt to gain a measure of the effort demanded by each task, response time for each stimulus was recorded. Results of the pilot study were used to modify stimuli and instruction sets so as to make the tasks as consistent as possible in terms of effort and input/output demands.

<u>Subjects</u>

Subjects were fifteen normal volunteers (7 males, 8 females) recruited from the Department of Clinical & Health Psychology. Subjects were screened by questionnaire to rule out neurological dysfunction, learning disability, and alcohol or drug abuse.

<u>Procedure</u>

All stimuli were presented on a Macintosh IIx (Apple Computer, Cupertino, CA) using the Psychlab software package (version 0.85; Gum, 1991). All stimuli were presented in a triple-spaced vertical fashion in 24 point Palatino font. The order of the five stimuli on each presentation slide was randomly determined, except in the syntactic generation condition as noted above. Likewise, the order in which the tasks were presented was randomly determined for each subject.

Prior to engaging in each task, subjects were trained according to predefined performance criteria. Criterion consisted of appropriate response to four consecutive sets of stimuli. After training, subjects were presented with 25 stimuli sets from each task. Response times for each set of stimuli were obtained by having the subject press the space bar upon completion of the required output. Sets of stimuli were presented sequentially upon completion of each previous set. There was a minimum of five minutes between each stimulation task during which training for the next task occurred.

In pilot study #1, the words used in the semantic association and syntactic generation tasks were chosen solely on the basis of frequency. Three frequency levels were arbitrarily created based upon the frequency ratings given by Francis and Kucera (1982), and the proportion of words from each frequency level was roughly equivalent between tasks. The stimuli used in the nonword condition were rearrangements of the letters in the words presented in the semantic association condition that conformed to English spelling rules. Efforts were made to ensure that words presented together in the semantic association condition have no obvious semantic link. Tasks were designed to be roughly equivalent in terms of input and required output, and constant visual presentation of the stimuli was used to minimize the memory requirements of the tasks.

The nonword rhyming task is meant to access the phonological component with a minimum of semantic or syntactic involvement. Psycholinguistically, the steps required to complete this task are visual analysis, grapheme-phoneme conversion, conceptual generation of phonemically similar output, motor programming of the generated output (phoneme level), and motor execution of the output.

The semantic association task is meant to access both the phonological and semantic components with a minimum of syntactic involvement. The psycholinguistic functions required by this task are visual analysis, identification of the stimulus by the visual input lexicon, access to the semantic system, generation of a semantically similar concept, identification of that concept in the speech output lexicon, motor programming of the generated output (phoneme level), and motor execution of the output. "Generation" in this task is subtly different from that required by the nonword rhyming task. In the nonword rhyming task, some phonemic qualities of the output are specified, but the subject is essentially asked to generate a novel combination of phonemes (within morphemic limits of the English language). In the semantic association task, however, the subject's task is more of an identification task, in that the subject identifies a pre-defined, semantically similar concept in his semantic network and produces the lexeme associated with that concept.

Finally, the syntactic generation task is meant to access phonological, semantic, and syntactic processing. Psycholinguistically, correct performance on this task demanded visual analysis, identification of the stimuli by the visual input lexicon, access to the semantic system, recognition of the semantic relationships between stimuli, recall of the specified syntactic frame, mapping of the syntactic frame onto the semantic relationship between stimuli, inflectional morphological alteration of individual items in the sentence as required by grammatical rules, motor programming of the generated output (phoneme level), and motor execution of the output. This task requires more working memory than the other tasks due to (1) the required memorization of the four sentence structures, and (2) the required perception/identification/semantic decoding of all five stimuli per set before successful performance of the task could begin.

Results

The time taken to complete each set of stimuli (hereafter referred to as response time, or RT) was recorded in milliseconds across tasks. Due to the extreme susceptibility of measures such as response time to outliers, the median RT for each task was computed for each subject. These data are presented in Figure 3-1. Repeated-measures analysis of variance (ANOVA) suggests there were significant differences between tasks ($p < .001$), with post-hoc analyses showing phonology>semantics>syntax (all at $p < .01$). Since effort was one of the primary factors to be controlled in the main study, and RT was felt to be an indirect index of effort, instructions and stimuli needed to be modified in order to make the tasks more congruent in terms of RT.

PILOT STUDY #2

Due to the finding of greater differences between tasks than were anticipated, it was decided that steps should be taken to insure greater comparability between the tasks in terms of performance time. As such, it was decided that imageability and concreteness would be added to frequency as criteria in choosing the stimuli to use in the semantic and syntactic tasks. This decision was based on findings which show that associative difficulty is negatively related to imageability, and, in turn, imagery and concreteness are positively associated with each other (Brown & Ure, 1969). Thus, it was posited that reaction time would be inversely correlated with the imagery and concreteness ratings of the stimuli. It was hoped that by reducing the time needed to generate semantic associates, the semantic association task and the syntactic generation task could be made more comparable. The motivation behind Pilot Study #2 was to generate stimuli utilizing these criteria. No measures were taken to influence the reaction time taken to perform the nonword rhyming task. Frequency ratings were available in Francis & Kucera (1982), and ratings of imageability for nouns were available from Toglia & Battig (1978). Unfortunately, ratings of the concreteness and imageability of verbs were not available. Thus, the purpose of the second pilot study was to generate ratings of imageability and concreteness for a wide variety of verbs.

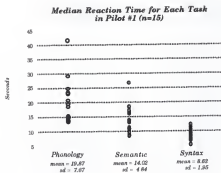**Median Reaction Time for Each Task
in Pilot #1 (n=15)**

Figure 3-1. Scatterplot of Median Response Times By Task for Pilot Study #1.

Subjects

Subjects were fourteen normal volunteers (4 males, 10 females) from the Departments of Clinical & Health Psychology and Speech and Language Pathology at the University of Florida in Gainesville, Florida. Subjects were screened by questionnaire to rule out neurological dysfunction and alcohol or drug abuse.

Procedure

Subjects were given a list of 246 verbs to rate in terms of both imageability and concreteness. The order of the verbs on each rating sheet was randomly determined in an effort to control for the effects of boredom. Subjects rated each attribute on a seven point scale. Imageability and concreteness instructions were those published by Paivio, Yuille, & Madigan (1968), modified slightly to apply to verbs rather than nouns. The imageability ratings generated by using these instructions are inversely related to associative difficulty (r = − 0.73: Brown & Ure, 1969). Verbs were selected for inclusion on the list based on pseudorandom selection from Francis & Kucera (1982). The method of selection was to take every fifth word that was used primarily as a verb. Directions may be found in Appendix A.

Results

The average ratings of imagery and concreteness given by the raters are presented in Appendix B. All words chosen for use in subsequent studies had imagery and concreteness ratings of five or more (nouns as rated by Toglia & Battig, 1978). As detailed in the methods section, words were also roughly balanced in terms of frequency ratings given by Francis & Kucera (1982).

PILOT #3

In order to minimize the contribution of brain activity involved in the motor act of vocalization to the data, it was decided that the optimal approach to take in the primary study was to have the subjects perform the tasks without vocalization. A primary purpose of Pilot #3 was to assess

the extent to which the difference between response times to previously-seen sets of stimuli and novel sets of stimuli could be used to gauge subject engagement in the task. Another goal was to use the data gathered from Pilot #2 to make the median RT more consistent across tasks by modifying the stimuli and instruction set.

Subjects

Subjects were ten normal volunteers (4 males, 6 females) from the Department of Clinical & Health Psychology (without overlap with the subjects used in Pilot #2). Screening for neurological dysfunction, learning disability, and substance abuse was done as previously mentioned.

Procedure

For each of the three stimulation tasks described above, subjects performed three separate trials. In trial #1, subjects were presented 20 sets of stimuli, and they were instructed to perform the task as described in Pilot #2 without vocalization. In trial #2, subjects were instructed to merely watch the 20 sets of stimuli on the screen flash by without engaging in the task. In trial #3, subjects were presented with 30 sets of stimuli, broken down as follows: 10 sets which had been presented during trial #1, 10 sets which had been presented in trial #2, and 10 novel stimuli. Trials #1 and #2 were counterbalanced in terms of order across subjects.

During trials #1 and #2, each set of stimuli was shown to the subject for 8.439 seconds, with the screen being blank for 0.200 seconds between sets. This interval represents the shortest median response time of the three tasks from Pilot #1. The shortest median response time was chosen in an attempt to ensure that subjects had to actively process the given task for the entire duration of the trial. During task #3, response time was monitored as in Pilot #1 so that comparisons could be made between types of stimuli. The types of sets of stimuli (engaged, not engaged, novel) were randomly arranged in trial #3.

Imageability and concreteness were taken into account when choosing the stimuli for the semantic and syntactic conditions. With frequency controlled as in pilot #1, only words with imagery

and concreteness ratings of five or more (on a scale of seven) were used. In addition, slight modifications were made to the instructions based on feedback and performances of earlier pilot subjects. Instructions may be found in Appendix C.

Results

Response times for each set of stimuli during the post-test period were recorded in milliseconds. As in Pilot #1, the median RT for each task was computed for each subject. The data are represented numerically in Table 3-1 and graphically in Figure 3-2.

In comparing the results of pilot studies #1 and #3, it is evident that the first goal of the study (i.e. to make the tasks more congruent in terms of RT) met with some success. Although differences in RT remained (repeated-measures ANOVA $F(2, 18)=21.14$, $p<.001$), visual inspection of the data shows that the differences in absolute RT between the tasks was reduced. In addition, informal debriefing of the subjects suggested that the phonology and syntax tasks were relatively equal in terms of subject estimation of difficulty, while the semantic task tended to be somewhat easier. Although the better comparability between the semantic association and syntactic generation tasks may be hypothesized to have resulted from the inclusion of imagery and concreteness ratings as selection criteria, it is unclear why the nonword rhyming task also became more comparable to the others in terms of RT.

The data in Table 3-1 and Figure 3-2 also depict the differences in RT within task according to the manipulation of the experimental stimulation. These analyses were carried out to see if these performances would be valid indicators of the subjects' "cognitive involvement" in the stimulation task. If this had proven to be the case, these indices could have been used to support the subjects attention to the stimulation task in the main study, since aural monitoring of the subjects' performance was precluded.

In the phonology task, repeated measures ANOVA suggested significant differences between RT to novel nonwords, nonwords which were seen but to which rhyming nonwords were not

intentionally generated, and nonwords to which rhyming nonwords were generated (p<.01). However, post-hoc analysis suggests that this difference was between novel nonwords and both of the other sets

Table 3-1
Average Median Reaction Times with Standard Deviations in Pilot Study #3

	Nonword Rhyming	Semantic Association	Syntactic Generation
Novel	$\bar{x}$ = 14.51 (2.71)	$\bar{x}$ = 11.54 (3.25)	$\bar{x}$ = 9.26 (2.43)
Passively Observed	$\bar{x}$ = 12.83 (2.89)	$\bar{x}$ = 10.98 (3.31)	$\bar{x}$ = 7.64 (2.13)
Actively Performed	$\bar{x}$ = 12.18 (2.71)	$\bar{x}$ = 11.17 (3.53)	$\bar{x}$ = 6.97 (1.13)

**Median Reaction Times
for Each Task in Pilot #3**
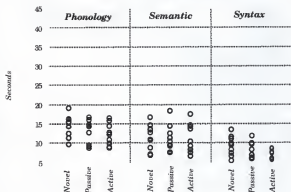
Figure 3-2. Scatterplot of Median Response Times By Task for Pilot Study #3.

Note: Novel denotes stimuli that were not seen until the post-test. Passive denotes stimuli which subjects were instructed to passively observe during the stimulation condition. Active denotes stimuli which subjects were instructed to actively engage according to the task instructions (see Appendix C). Means and standard deviations of these data are listed in Table 2-1.

of nonwords; nonwords to which the subject had been exposed did not differ in terms of RT regardless of the generation of intentional generation of nonwords.

In the semantic task, repeated-measures ANOVA suggested that there were no significant differences in the average median time it took to generate semantic associates to real words, regardless of previous exposure to the stimuli.

In the syntax task, repeated-measures ANOVA suggested that there were significant differences in RT across exposure conditions ($p < .001$). As with the phonology task, however, post-hoc analyses suggest that these differences were only significant when comparing novel stimuli to those which had been seen previously. There was no difference in RT when comparing those stimuli which were passively observed to those in which the subject actively constructed sentences and questions.

The results of Pilot #3 clearly indicate that the difference in RT between "passively observed" stimuli and "actively-engaged" stimuli would not be a valid indicator of silent engagement in the activation task. Thus, it was decided that we would attempt to increase motivation to attend to the stimuli during the stimulation task by offering a reward for good performance on a post-test (see below).

PRIMARY STUDY

Subjects

Subjects were twelve normal male, right-handed volunteers (see Table 3-2). Subjects were recruited by an ad in the student newspaper of the University of Florida in Gainesville, Florida. Screening for neurological dysfunction, learning disability, and substance abuse was done as described in Pilot #1. Handedness was assessed using items derived by Raczkowski, Kalat, & Nebes (1973). Informed consent was obtained. Before the initial task performance, subjects were administered the Vocabulary subtest from the Wechsler Adult Intelligence Scale – Revised (WAIS-R). This scale is the most reliable subtest on the WAIS-R, is the best measure of g (i.e. "general intelligence"), and is correlated highly with Verbal IQ ($r = 0.85$) and Full-Scale IQ ($r = 0.81$) (Sattler, 1988).

Subjects were each paid $25 for the completion of each of three SPECT scans and an MR scan as well as an additional $25 for completion of the study, for a total of $125. Subjects were mailed their payment upon completion of their participation in the study. In addition, each subject was paid $10.00 per SPECT scan as a motivational tool as will be explained below.

<u>Apparatus</u>

A full description of the scanning apparatus and materials has been given elsewhere (Shukla, Honeyman, Crosson, Williams, & Nadeau, in press). Briefly, MR and SPECT measurements were performed at the Veteran's Administration Hospital in Gainesville, Florida. MR measurements were performed with a Siemens Magnetom 1.5 Tesla (Iselin, NJ). All SPECT measurements were performed with a three-headed SPECT scanner (TRIAD-88, Trionix Research Laboratory, Twinsburg, OH). This system has an in-plane (transverse) reconstruction resolution of 9.3 mm full width-half maximum (FWHM) and a between-plane (axial) resolution of 9.3 mm FWHM at the center of the field of view. 20 mCi injections of technetium-99m-d,l-hexamethylpropyleneamine oxime ([^{99m}Tc]-d,l-HM-PAO) were administered prior to each SPECT scan. Studies of the pharmacokinetics of [^{99m}Tc]-d,l-HM-PAO, a lipophilic tracer, indicate that once inside the brain, it is rapidly converted to a hydrophilic form that is maintained for many hours. However, the tracer is not trapped instantly once inside the brain, thus resulting in a significant amount of backdiffusion into the bloodstream (Andersen, Friberg, Schmidt, & Hasselbach, 1988). It has been shown that, following intracarotid injection, the total hemispheric counts reach a peak within 40 - 60 seconds and then decline exponentially to a steady-state level of approximately 40-50% of peak activity after about 10 minutes. After this time, activity decreases at a rate of approximately 0.4% per hour (Andersen et al., 1988; Lassen, Andersen, Friberg, & Paulson, 1988).

In order to aid in orientation of and localization within the scans, plastic molding material (JKR Laboratories, Inc. XL-100 Impression System, Wichita, KS) was used to make custom-fitted casings for copper sulfate solution markers for MR and cobalt-57 markers for SPECT. These casings were placed within each ear and on the glabella. As the SPECT apparatus is capable of rotating

Table 3-2
Primary Study Sample Characteristics

N = 12 subjects

	Mean	S.D.	Range
Age	21.00	2.30	18 – 27
Education	14.58	1.50	12 – 18
WAIS-R Vocab	14.33	2.15	11 – 18

reconstructions three-dimensionally, the matching of marker configuration to that seen in the MR
enables accurate SPECT-slice-to-MR-slice matching, thus insuring that localization is not confounded
by rotational factors.

The stimuli for the training and test conditions (to be described below) were presented using a
Macintosh SE (Apple Computer, Cupertino, CA) with the Psychlab software package in a small, quiet
room in the department of Nuclear Medicine at the Veteran's Administration Medical Center in
Gainesville, Florida. The stimuli for the activation condition were presented running the same
software on a Macintosh IIx in the same room as the SPECT scanner. This room was chosen for its
constant level of background noise (from the fans that cool the scanner and associated computer).
Subjects' responses during the test condition were recorded on Sony metal audiocassette tapes using a
Sony TC-D5M audiocassette recorder and a Sony ECM101-SM stereo microphone.

Image Analysis

MR slices were 7 mm thick, with a 7 mm center to center distance. Pixel size on the MR is
0.9014 mm^2. SPECT slices were reconstructed so as to be 7.12 mm thick, with a center to center
distance of 7.12 mm. Pixel size in the acquired scans on the SPECT is 3.56 x 3.56 mm. Acquired
SPECT images were converted from 64 x 64 pixel images to 128 x 128 pixel images, thereby reducing
interpolated pixel size to 1.78 x 1.78 mm. Analyses are based on MR and SPECT slices acquired from
the bottom marker level to the top of the brain. SPECT and MR images were rotated such that all three
markers were in the same plane of view. This plane of view corresponds approximately to the A4
angle described by Damasio & Damasio (1989).

Due to the nonlinear relationship between rCBF and HM-PAO distribution obtained in an
uncorrected SPECT scan utilizing [^{99m}Tc]-d,l-HM-PAO as a tracer, images were corrected using the
method described by Lassen et al. (1988), using whole-brain as the reference region and α = 1.2.
Whole brain counts were determined by adding the counts in four equally spaced slices beginning just
above gyrus rectus and continuing to just above the lateral ventricles. This sum was then divided by
the total number of brain pixels in those four slices to yield an index of the average counts per pixel.

Brain pixels were defined in the following manner: first, an outline was drawn around the identified MR slice of interest by the experimenter; next, the matching SPECT slice (previously corrected for rotational factors using the markers) was superimposed upon this outline; and finally, those pixels falling within the outline were considered to be brain pixels. Pilot data have shown this index to be an extremely consistent and accurate estimation of the whole-brain average obtained by using all brain slices.

Slices in which the regions of interest (ROI's) located were identified by referencing the patient's MR to a neuroanatomical atlas (Damasio & Damasio, 1989). ROI locations are noted in Figure 3-3. Once the region was identified on the MR, the number of slices between this slice and the slice most clearly showing the markers was determined. This number was then used to locate the analogous SPECT image.

In order to accurately localize the regions of interest (ROI's) within the SPECT image, two methods were used. For cortical ROI's, an algorithm was used in which two of the three coordinates of the ROI were referenced to the subject's MR scan, and the third was located in the center of cortex as indicated by activity level. This algorithm is designed so as to maximize the strengths of the respective types of scans: MR for accurate localization, and SPECT for assessment of activity level in a given cortical area. Upon location of the ROI in the atlas, the anterior and posterior points of the region of interest were measured and the proportional distances of the anterior and posterior points of the ROI to the distance between the frontal and occipital poles was computed. In translating the MR coordinates to the SPECT scan, the formulae found in figure 3-4 were used to determine the proportional distances of the anterior and posterior points of the ROI to the distance between the frontal and occipital poles.

These coordinates were located on the patient's MR scan so that minor adjustments could be made if necessary. After the anterior and posterior SPECT coordinates were determined, two 8.9mm x 8.9mm nonoverlapping ROI's were placed in the y-axis center of the ROI. The x-coordinate for the center of the ROI was determined by inspecting the x-values along the predefined y-coordinate and choosing the center of the five x-values within the confines of the ROI with the highest total value. It is felt that this represents the center of the gray matter of interest. This algorithm simultaneously
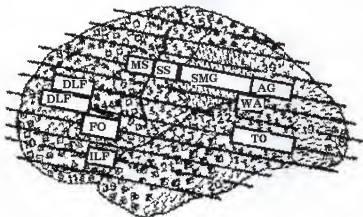
Abbreviations:

ILF	=	Inferior Lateral Frontal
FO	=	Frontal Operculum
TO	=	Temporo-Occipital Association Cortex
DLF	=	Dorsolateral Prefrontal
WA	=	Wernicke's Area
SMG	=	Supramarginal Gyrus
AG	=	Angular Gyrus
MS	=	Motor Strip
SS	=	Sensory Strip

Figure 3-3. Location of Regions of Interest.
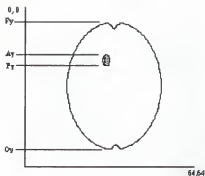
$$D_a = \quad (A_y - F_y) / (O_y - F_y) \qquad\qquad D_p = \quad (P_y - F_y) / (O_y - F_y)$$

where D_a and D_p = distance of the anterior and posterior points,

respectively, of the ROI from the frontal

pole, expressed as a proportion of the frontal pole-

occipital pole distance,

A_y = y-coordinate of the anterior point of the

ROI,

P_y = y-coordinate of the posterior point of the

ROI,

F_y = y-coordinate of the frontal pole,

O_y = y-coordinate of the occipital pole.

Figure 3-4. Localization Formulae.

maximizes structural imaging's advantages in anatomical localization and functional neuroimaging's advantages in locating the areas of greatest change in rCBF. This method has a number of advantages: (1) it minimizes variability inherent in outlining ROI's in the cortical regions, and (2) it enhances flexibility in matching to nonsquare structures, as ROI's may be placed in any configuration as long as they do not overlap or exceed the boundaries of the region as defined by MR,(3) it is systematic and reproducible, (4) it eliminates the variability inherent in combining data across subjects, and (5) it addresses the concern of intrasubject image misalignment (with subsequent errors in estimation of change in rCBF) discussed by Phillips et al. (1990).

Since subcortical structures are not defined in the neuroanatomical atlas chosen for this study, subcortical ROI's were identified using a procedure analogous to the one used to arrive a whole-brain counts. First, the experimenter outlined the ROI on the subject's MR. The matching SPECT slice was then superimposed on the MR slice, and counts were taken from the outlined area.

Procedure

After responding by phone to an advertisement placed in the school newspaper at the University of Florida, subjects were contacted by phone and administered a brief screening questionnaire(as used in the Pilot #3) to insure that the subjects were right-handed and rule out neurological dysfunction, learning disability, and substance abuse. Those subjects who passed screening were then scheduled to come in for an informed consent meeting in which the study was explained and questions were answered by the principal investigator. Informed consent was obtained from those subjects still interested in participation.

Due to the half-life of the tracer used, SPECT scans were scheduled to be no closer than four days apart in order to assure total washout of activity from one scan to the next. The majority of scans were one week apart, with one subject having two scans four days apart and three subjects having scans more than one week apart. The order of scans was counterbalanced across subjects, and each subject completed all three tasks. One subject was excluded from the data analysis due to an old lesion

in the right head of the caudate nucleus discovered on the MR scan which was completed for the purposes of this study.

For each experimental session, subjects were trained to criterion before engaging in the stimulation task. This was done in an attempt to familiarize the subjects with the demands of each task as well as to minimize the potential effects of task novelty (Damasio, 1985). Criteria consisted of four consecutive sets of stimuli performed without error. Adequate performance is defined in the different tasks as (1) successfully generating a rhyming nonword for each stimulus, (2) successfully generating a semantic associate for each stimulus, and (3) successfully generating a sentence of the specified structure with the given stimuli. Although exact times were not obtained, it is estimated that training for the phonology task took approximately 5 minutes, training for the semantic task approximately 3 minutes, and training for the syntactic task approximately 15 minutes on average. During the stimulation task, subjects were presented with 64 stimulus sets (each on-screen for 6.966 seconds), with 0.200 seconds of blank screen between each set. Following the stimulation task, subjects were presented with a post-test of 20 sets of stimuli (10 novel, 10 presented during the stimulation task) during which reaction time was recorded for each set of stimuli. Finally, subjects were asked to rate the difficulty of the task performed that day on a 100 mm visual analog scale. SPECT scanning was performed after rating the difficulty of the task. On one of the subject's three visits, MR scanning was performed before SPECT scanning. Instructions for each task may be found in Appendix D, while stimuli may be found in Appendix E..

Placement of the IV line was done prior to initiation of training by a technician in Nuclear Medicine. The apparatus was arranged such that the heparin lock into which the radionuclide would be injected was behind the subject, and tubing was arranged so as to minimize movement of the IV upon injection. This was done in an effort to minimize distraction of the patient from the experimental task at the time of injection, as subject reports during previous pilot research suggested that the movement of the heparin lock is more distracting than is the injection of the isotope. Informal questioning of the subjects after completion of the study indicated that this was largely successful, with most of the subjects reporting that they did not notice the injection occurring. Those that did notice stated that the

injection did not present a major distraction to their performance of the task. The injection was performed 90 seconds after the stimulation task was begun. The preinjection stimuli presentations are given to insure patient understanding of the task and ongoing cognitive activity at the onset of tracer uptake by the brain. Stimuli were continued for approximately six minutes after injection. Recent findings suggest that a five-minute envelope should be sufficient time for the tracer pattern within the brain to be established (Woods et al., 1990).

As mentioned earlier, subjects performed the activation task silently in an attempt to minimize the contribution of regions involved in the motor execution of language. In order to promote subject engagement in the task for the entire duration of the stimulation period, a number of measures were taken. First, the shortest average median response time in pilot #3 (Syntax-Engaged: 6.966 seconds) was chosen as the time interval for which the stimuli would remain on the screen. The median time was chosen in order to ensure 1) that there would be very little (if any) time between stimulus sets in which a processing demand was not placed upon the subject, and 2) that the same interval could be used across tasks, so that subjects would be presented with an equal number of stimuli in all conditions.

The other measure which was taken in order to promote subject compliance was a deception aimed at increasing subject motivation. Subjects were told that each session would be broken down into three components: 1) introduction to the task, 2) silent practice of the task, and 3) test of task performance. Subjects were instructed that, although the investigators were interested what was going on in the brain during silent practice of the task, the primary thrust of the experiment was to determine the extent to which silent practice could improve speed of response in the three language tasks. Subjects were told that previous research had shown that silent practice improves the speed of response in the tasks, but only if the practice was done continuously for approximately eight minutes. Subjects were told that if their average response times to the sets that they would see during the silent practice were faster than their response times to the novel sets that they would also see in the post-test (as should be expected with continuous silent practice of the task), then they would receive an extra ten

dollars at the end of the experimental session that day. Reaction times were examined while subjects were being scanned, but subjects were awarded the $10.00 regardless of their performance.

Debriefing

Following each stimulation condition, subjects were asked if they had any difficulties concentrating on the task at hand. Following the final stimulation condition, each subject was given an opportunity to ask any questions that he might have had concerning the procedures or experimental hypotheses.

CHAPTER IV

RESULTS

Data Analytic Strategy

All statistical analyses were performed with SYSTAT 5.2 for the Macintosh (Wilkinson,

1992). Following Friston et al. (1990), functional neuroimaging data were analyzed via analysis of

covariance (ANCOVA), with whole-brain counts as the covariate. As detailed earlier, this is done in

an effort to control for systematic factors affecting whole-brain counts which are unrelated to

differences engendered by the cognitive activation. There are a number of differences between this

analysis and those of Friston et al., however. At a very basic level, the data are acquired differently, in

that this study uses an *a priori* region-of-interest approach, as opposed to Friston et al.'s pixel-by-pixel

analysis. Thus, the data in this study are referenced to individual MR scans on which ROI's are

located, as opposed to a standardized, per-pixel analytical approach in which anatomical variability is

presumed to be controlled smoothing and image standardization.

From a statistical perspective, this analysis was performed in a repeated-measures framework,

since within-subject changes in ROI activities were the primary variables of interest. This analysis was

done in the context of a multiple regression analysis as detailed by Cohen and Cohen (1983). The

primary advantage of multiple regression format is that it allows for the determination of effect sizes of

both covariates and independent variables. Given the great variability between methodologies in the

imaging literature and the low statistical power inherent in all of them, it was felt that it would be

helpful to obtain some measure of the magnitude of effect that these sorts of activation paradigms have

on regional counts. The effect size of an independent variable, or that proportion of the variance in the

dependent variable accounted for by the independent variable while controlling for the contributions of

other variables, tends to be a much more stable index of effect strength than does statistical

significance, primarily due to the heavy reliance of traditional F-ratios on the number of subjects

(Cohen & Cohen, 1983; Rosenthal & Rosnow, 1989). Furthermore, effect size is a more applicable measure to guiding further research efforts, as it is easily incorporated into (1) estimates of the number of subjects needed to achieve a given power, and (2) meta-analytical techniques which examine the variance of effect strengths across studies in an effort to get a better grasp on the magnitude of phenomena being observed.

A critical assumption inherent in ANCOVA designs is the lack of a significant relationship between the dependent variable and the interaction of the independent variable and the covariate, or *homogeneity of regression* of the dependent variable on the covariate across levels of the independent variable (Cohen & Cohen, 1983). Stated more simply in terms of the current study, it must be shown that the extent to which whole-brain counts may be used to accurately predict regional counts must not vary according to the task. This assumption is checked out by making sure that the interaction term (Whole-brain counts)x(Activation Task) does not contribute significantly to the variance seen in regional counts. This assumption was confirmed in all ANCOVA analyses performed in this study.

As an aid to visual analysis of the adjusted data used in the analyses, individual adjusted ROI values were generated in the following manner. First, the multiple regression ANCOVA described above was performed. This equation had the following conceptual formula:

$$\text{Regional Counts} = \text{Constant} + \beta 1(\text{Subject}) + \beta 2(\text{Whole Brain Counts}) + \beta 3(\text{Task}) + \text{error}$$

Computationally, the categorical variables SUBJECT and TASK were broken down in n-1 dichotic dummy variables (11 for subject, 2 for task). Regression analysis yielded the beta-weights for each dummy variable and whole brain counts. Adjusted ROI values were then determined by the following conceptual equation:

$$\text{Adjusted ROI counts} = \text{Observed ROI counts} - \text{Constant} - \beta 1(\text{Subject}) - \beta 2(\text{Whole Brain Counts}) + \text{error}$$

Again, computationally, SUBJECT was broken down into 11 dichotic dummy variables, each with its associated beta-weight.

<u>Investigation of the Effect of Cognitive Effort</u>

A priority in the analysis of the data from the main study was to rule out the possibility that the amount of cognitive effort demanded by each task played a significant role in influencing the results. Given the apparent discrepancy between subjective experience of task difficulty and RT that was noticed in Pilot #3, subjects in the Main Study were asked to rate the difficulty of each task on a 100 mm visual analog scale (VAS) immediately after completion of the post-test. Results of these ratings are presented in Figure 4-1. Repeated-measures ANOVA suggests that these ratings do differ significantly (p<.05), but post-hoc analyses suggest that the only significant difference lay in the comparison between the ratings of the phonology and semantic tasks (p<.04).

The relationship between difficulty rating and response time to novel stimuli is depicted in Figure 4-2. As can be seen, these two variables are significantly related (p<.01). Correlational analyses suggest that neither of these variables contribute significantly to the variation seen in global- and regional-cerebral blood flow values, however (see Appendix F).

<u>Tests of Hypotheses</u>

<u>Across Task Analyses</u>

It was predicted that there would be no systematic effect of type of cognitive activation (hereafter referred to as TASK) on whole-brain counts. This prediction was supported, in that the null hypothesis of no difference between tasks could not be rejected in a repeated measures ANOVA ($F[2,22] = 0.873$, $p = 0.432$).

It was predicted that ROIs in the right hemisphere would not be systematically affected by TASK. While this prediction was supported for right-hemisphere homologs of traditionally defined "language-related" ROI's, repeated-measures ANCOVA did reveal a significant effect for TASK in the right motor cortex ($F[2,21] = 3.599$, p<.05). These data are depicted graphically in Figure 4-3. The
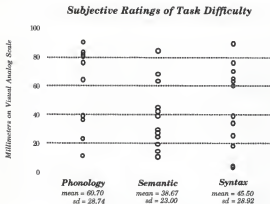
Figure 4-1. Subjective Ratings of Task Difficulty on 100mm Visual Analog Scale.
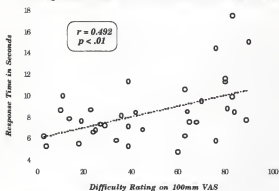
Figure 4-2. Relationship between Subjective Rating of Task Difficulty and Reaction Time.

activity in the semantic condition is markedly lower than in the other two conditions, although this difference is statistically significant only in the comparison of the syntax and semantic conditions (p<.04).

It was predicted that the activity seen in the left posterior superior temporal region (Wernicke's area) would be significantly greater in the semantic and syntactic tasks than it will be during the phonology task. These data are depicted in Figure 4-4. While the activity in the region is certainly notably higher in the semantic condition than in the phonological condition, the prediction was obviously not supported in the syntax-phonology comparison. In fact, the only statistically significant difference is in the comparison of the semantic and syntax conditions (t = 3.426, p<.01). Of note, left Wernicke's area is the only cortical region in which activity is notably greater during the semantic task than during either of the other two tasks. Scatterplots comparing the activity of regions across hemispheres and tasks may be found in Appendix G.

It was predicted that activity in left dorsolateral prefrontal cortex would be significantly greater in the syntactic task than in the other two tasks. These data are depicted in Figures 4-5 and 4-6. This prediction was supported in neither of the dorsolateral prefrontal ROI's that were examined. While there was a relatively weak effect of TASK on the more inferior of the two ROI's on the left, this seemed to be more related to the increased activity during the phonological task than during the syntactic task. Effect sizes of TASK on the various ROI's are depicted in Figure 4-7.

It was predicted that the activity in regions typically cited as being involved in language functioning would be highly intercorrelated across tasks. This prediction was explored by examining partial correlations (controlling for whole-brain counts) between these regions. This prediction was not supported, particularly in the relationships between anterior and posterior regions. Rather, the strongest patterns of correlation appear between frontal regions both within and across hemispheres, particularly for the prefrontal regions (see Table 4-1). In addition, consistently high intercorrelations are seen between basal ganglia structures and between the left and right thalamic nuclei. A complete listing of partial correlations between variables may be found in Appendix H.

Right Motor Cortex (s.8)
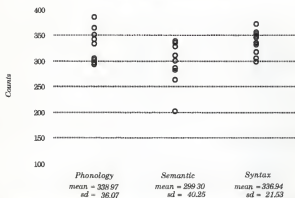
Figure 4-3. Scatterplot of Counts in Right Motor Cortex Across Tasks (at the level of A4 slice 8 in Damasio & Damasio [1989]).
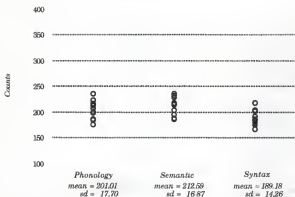
Figure 4-4. Scatterplot of Counts in Left Wernicke's Area Across Tasks.
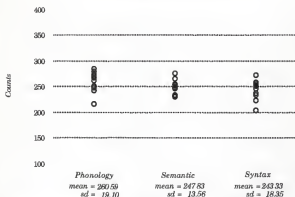
Figure 4-5. Scatterplot of Counts in Left Dorsolateral Frontal Cortex Across Tasks (at the level of A4 slice 5 in Damasio & Damasio [1989]).
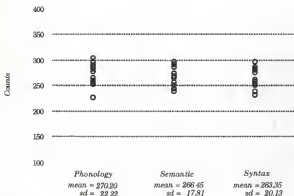
Figure 4-6. Scatterplot of Counts in Left Dorsolateral Frontal Cortex Across Tasks (at the level of A4 slice 6 in Damasio & Damasio [1989]).
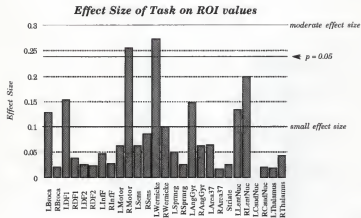
Figure 4-7. Bar Graph of Effect Sizes of TASK on Activity (counts) in each ROI

Table 4-1
Partial Correlations of Frontal and Subcortical Regions

	LBroca	LDLF5	LDLF6	LInFront	LMotor
LBroca					
LDLF5	0.643*				
LDLF6	0.453	0.803**			
LInFront	0.556	0.259	-0.180		
LMotor	0.457	0.603	0.576*	-0.055	
RBroca	0.426				
RDLF5		0.795**			
RDLF6			0.825***	0.847***	
RInFront					
RMotor					0.791**

	RBroca	RDLF5	RDLF6	RInFront
RBroca				
RDLF5	0.784**			
RDLF6	0.592*	0.899***		
RInFront	0.248	0.174	0.057	
RMotor	0.570	0.732**	0.778***	-0.298

	LCaud	LLnt	LThal	RCaud	RLnt
LCaud					
LLnt	0.848***				
LThal	0.327	0.508			
RCaud	0.725**				
RLnt		0.746**		0.769**	
RThal			0.823***	0.391	0.039

Note. $* = p<.05$; $** = p<.01$; $*** = p<.001$

Codebook[†]:

L	= left
R	= right
Broca	= frontal opercular region (Broca's area)
DLF5	= dorsolateral frontal region (Areas 9 and 46 other than anterior pole in slice 5)
DLF6	= dorsolateral frontal region (Areas 9 and 46 other than anterior pole in slice 6)
InFront	= inferior frontal region
Motor	= primary motor region

[†]: All regions located on the A4 template provided by Damasio & Damasio (1989), p. 190-191.

Within Task Predictions

It was predicted that rCBF during each task would be marked by significant asymmetry in dorsolateral prefrontal cortex and frontal operculum. Figure 4-8 depicts the asymmetry observed in each task according to the significance of the asymmetry. While the left frontal operculum consistently shows greater activity than does its right-sided homologue, the same cannot be said of left dorsolateral prefrontal cortex.

Significant asymmetry was also predicted to occur in posterior superior temporal regions during the semantic and syntactic tasks. It was predicted that this asymmetry would occur due to the demand for comprehension of open-class items inherent to both tasks. As within task hypothesis #1, this prediction received partial support, as significantly greater activity was observed in left Wernicke's area than in its right hemisphere homologue during the semantic task. However, this did not occur during the syntax task.

In general, the asymmetries present a great deal of interesting information. In particular, the consistency of the left-right asymmetry in frontal opercular (Broca's area) and inferior temporo-occipital association cortices (Brodmann's area 37) across tasks is striking. Specific asymmetries were seen within the task as well. During the nonword rhyming task, the angular gyrus region was significantly more active on the left (see Figure 4-8). During the semantic association task, asymmetry was observed in both Wernicke's area and the lenticular nuclei. Finally, during the syntactic generation task, there was a remarkable lack of asymmetry in regions other than the previously noted asymmetries in frontal opercular and inferior temporo-occipital association cortices.
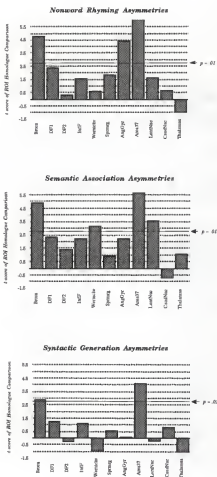
Figure 4-8. Asymmetry of rCBF in each task as reflected in t-scores from paired comparisons.

CHAPTER V

DISCUSSION AND CONCLUSIONS

In this study, a number of predictions were made about the patterns of rCBF that would be seen during the performance of certain cognitive activation tasks, and hypotheses were ventured about how these patterns would change between conditions. In discussing the ramifications of these findings, a number of factors which influence the results bear consideration. The first of these is the relative merits and drawbacks of the method of image analysis that was chosen.

In review, ROI's were chosen *a priori* based on findings in both the lesion and functional neuroimaging literatures. For cortical regions, the anterior and posterior boundaries of these regions were located relative to the anterior and posterior poles of a given transverse MR cut in a neuroanatomical atlas (Damasio & Damasio, 1989), and these coordinates were then proportionally transferred to each subject's MR. Given no obvious errors in localization to this point, these coordinates are then used to locate a 8.9 mm x 17.8 mm region in the middle of each ROI on the subject's SPECT scans, in conjunction with x-axis activity levels found in the SPECT scans themselves. Subcortical ROI's were drawn on the appropriate slices and the SPECT slices were superimposed on these drawing to obtain estimates of activity. Values were taken from these ROI's and then combined with the analogous data from other subjects in forming the database upon which the analyses were performed.

This approach has a number of advantages in relation to other methodologies. First and foremost, the approach is theoretically driven and much less susceptible to the overinterpretation of outliers than the subtraction and pixel-by-pixel analysis algorithms. This resistance to outliers is also abetted by the use of ROI's of a predefined size. In addition, the reference of both the SPECT data and the neuroanatomical atlas to each subject MR scan minimizes the effect of interindividual differences in brain morphology in defining ROI's.

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The *a priori* sizing and placement of ROI's can be a two-edged sword, however. The same anatomical findings which cast doubt on the validity of intersubject averaging of functional images also give one pause in accepting the accuracy of locating a region in the same proportional space across individual MR scans. Likewise, even if we were to accept the accuracy of the localization of the identical anatomical region across subjects, one is still left with the almost-certain variation in "functional anatomy" within the structures; thus, one must come to terms with the assumption that a given region will receive activation (or inhibition) into its afferent terminals in a manner that is similar across subjects. While the relative success of neuropsychology/behavioral neurology in general and classical aphasiology in particular suggests that this is probably a worthwhile assumption to make on a gross level, the assumption becomes more tenuous the closer one gets to the finer aspects of anatomy and physiology.

On a more practical level, algorithms using local maxima and minima (i.e. single pixels) as indices of rCBF take a more empirical, less theoretical approach and are inherently much less conservative than ROI algorithms. This decreased conservatism usually guarantees significant results which can almost always be rationalized in a *post-hoc* fashion. Difficulties arise in the interpretation of these findings, however. While these smaller indices are much less likely to be confounded by the combination of areas of different flow levels or functional significance than are larger ROI's, this increased specificity comes at the price of less certainty about the identity of what exactly it is that one is observing, in that one becomes more susceptible to outliers and variability resulting from misalignment and/or anatomical/physiological variability between subjects (when combining data from different brains). Although still far from perfect, the intrasubject, ROI-based approach basing localization on a combination of structural and functional neuroimaging data that was used in this study addresses these concerns more completely than do the pixel-by-pixel image standardization techniques.

Another factor to keep in mind is the nature of the data yielded in any imaging study. As stressed early in the literature review, the changes that one observes in comparing functional images are inherently systemic measures, since they reflect activity *at the synaptic level* in a given region, not

activity in the cell bodies themselves. Thus, these images represent a composite of (1) the change in afferent input (excitatory and inhibitory) into a region from other regions of the brain, and (2) the change in intraregional dendritic activity. As the magnitude and variability in this ratio across regions is currently unknown, interpretation of the data is a complex undertaking. Certainly, however, one must be conversant with both the neuroanatomical connections in and the theoretical functional significance of a given region, as it is only through examination of these factors in conjunction that one will be able to determine which areas are truly being "activated" and which are being "inhibited." Unfortunately, conclusions which may be drawn about "neural activity" are limited by the inescapable confounds of 1) the complexity of neural interconnections and 2) the time intervals over which activity in these connections are integrated in functional imaging studies.

Thus, keeping these considerations in mind, we now turn to the interpretation of the results. Many of the hypotheses were confirmed to some degree, lending convergent validity to the interpretation of these findings. The lack of significant global change in between relatively high-level cognitive stimulation tasks is replicated in this study. Given the consistency of this finding across laboratories, it is felt that the intrasubject asymmetry data provides a more powerful indication of specific regions which are preferentially involved in given cognitive operations. As predicted, the effect of the type of language stimulation on the right hemisphere homologues of "traditional language areas" was very minimal and always less than the effect seen on the left-hemisphere region. The most consistently asymmetrical perisylvian region examined was the frontal opercular cortex.

When looking both within and across tasks, it is evident that the cognitive demands of the semantic association task place a higher premium on the functions carried out in the left posterior superior temporal region than do the other tasks. Given the complexity of cognitive demands of the task and the multiplicity of the psycholinguistic roles that this region is assumed to play based on the lesion literature, it is difficult to hypothesize exactly what processes are indicated by this activation. If the activation was due primarily to phonemic sequencing, one would expect the asymmetry to be present in the nonword generation condition as well. This was not the case. Rather, significant asymmetry in this region was seen only during the semantic association task. Although this task was

distinct from the others in terms of the amount of new lexical-semantic material presented (approximately 40% more open-class items than were presented in the syntactic structuring task), the major distinction of the semantic association task was the demand for generation of open-class items. Thus, even with the potential confound of input and output lexical-semantic demands, it is obvious that the left posterior superior temporal region is involved in these lexical-semantic processes in a way that is not seen in the other two tasks. Unlike the data of Wise and colleagues, these data are not confounded by the task being auditory in nature.

This finding is important as it relates to the controversy about the function of the left inferior lateral prefrontal cortex. Clearly, the notion that an explicit demand for semantic processing of single words will significantly increase rCBF in this region is not supported by these data. This notion was investigated by directly comparing the pattern of activation seen during the nonword generation task to that seen during the semantic association task. In addition, the lack of a significant asymmetry in this region during the performance on any of the tasks casts doubt on its role in semantic processing. Although this result would appear at first glance to be contradictory to the available findings from other studies, this is not the case. In fact, the only other *direct* comparison of tasks involving the perception/higher processing of nonwords to the perception/higher processing of real words was performed by Wise and his colleagues (1991), who also reported no differences in this region. Petersen and colleagues (1990) indirectly supported their contention of semantic processing in the left inferior lateral prefrontal region by comparing both passive reading of nonwords and real words to observation of false font strings, respectively, and pointing out that the rCBF in this region increased significantly in only the latter comparison. Zatorre and colleagues (1992), conversely, were unable to differentiate semantic from other linguistic forms of processing due to the nature of their stimuli. Thus, the available data suggest that whatever process is reflected by a change in rCBF in this region is not strongly enough related to semantic processing to differentiate itself from tasks requiring the observation or auditory perception of individual morphemes. Thus, the functional imaging and lesion literatures have yet to produce a consistent picture of exactly what role this region plays in language,

whether it is language specific or whether it relates to "higher" processes important to the tasks which have been used in the experimental paradigms to date.

The ways in which the hypotheses were not supported is perhaps even more interesting than the accurate predictions. In particular, the information gained about the syntax task was very surprising. Going into the study, it was expected that this task would be the most demanding, as correct task performance demanded phonological, semantic, and grammatical skills. However, as the behavioral results (primarily reaction time) began to emerge, it was evident that the processes being tapped by this task were different in qualitative as well as quantitative ways. Perhaps most importantly, the number of "objects" or "goals" was less per each set of stimuli in the syntax task than in the other tasks despite the presented amount of lexical information being held constant. In other words, while both the nonword rhyming and semantic association tasks demanded five separate responses which were relatively unrelated to each other, the syntax task demanded one integrated response. Thus, despite the fact that the absolute number of generated words may have been slightly higher in the syntax task, the "conceptual output" (i.e. one sentence) was lower. It is believed that it is the decreased conceptual output demand that led to the consistently faster response times in the syntax task than in the other tasks.

The other strikingly surprising finding was the relative lack of asymmetry of rCBF during the syntactic generation task. Although the frontal opercular and temporo-occipital asymmetries seen during the other tasks were present in this task as well, there was no asymmetry unique to the syntactic generation task, and all asymmetries seemed decreased relative to those seen during the other tasks. Although this finding certainly does not mean that few regions changed in terms of rCBF, as a symmetrical change would also lead to a lack of asymmetry, but the consistency with which rCBF in the left dorsolateral frontal cortex has been shown to increase proportionally more than the homologous region on the right in verbal generation tasks makes it surprising that such an asymmetry would fail to appear during this task. Put simply, it is felt that this is a practice effect. Although the conceptual output demanded by the task was smaller in magnitude, it was more complex in nature, especially given the generation of the non-canonical sentence structures that were used. Thus, another

major behavioral difference between the tasks was the amount of time it took to train the subjects to do each task. Although the exact discrepancy between conditions in terms of training time was not determined, it is estimated that subjects received an average of at least three times more practice on this task than on the others in order to reach the criterion performance indicating relative comfort with task demands. Unfortunately, it has been shown that one effect of practicing a task is the attenuation of rCBF response observable on SPET (Larsen et al., 1978), and the improved temporal and spatial resolution of PET suggests that the rCBF pattern may change qualitatively as well (Raichle, 1991). It is felt that this is exactly the process that one is observing when examining the distribution of rCBF as determined by SPECT in the syntax task. Such a dynamic would account for both (1) the apparent decrease in rCBF in language areas when comparing the highest-level language task to the other tasks and (2) the startling lack of asymmetry in these areas within the task. In terms of the explicitly-stated hypotheses, this dynamic could account for both left Wernicke's and left dorsolateral prefrontal cortices registering their fewest counts during the syntax task. This dynamic is consistent with theoretical formulations of frontal lobe function which postulate that prefrontal cortical function is critical to the efficient processing of novel stimuli (Damasio, 1985). The lack of asymmetry in the left posterior temporal region that might have been expected based on the use of meaningful words may be related to the fact that the task required no generation of open-class items, as did the semantic task.

A surprising finding which is less easily reconciled with recent imaging or neurolinguistic findings is the magnitude of the effect size seen in right motor and subcortical (lenticular) regions. The finding that right motor cortex located at approximately arm level would receive lower levels of afferent input in the semantic task than in the other two tasks is quite puzzling. Likewise, the processes occurring in the right lenticular region are not readily apparent. The latter region is more difficult to interpret in general due to the inclusion of two distinct nuclei (or three, if one wished to break the globus pallidus into its lateral and medial components) in the ROI, one of which is known to have inhibitory effects upon the other (Crosson, 1992). However, research suggests that if the lenticular nuclei play any role in language, it is certainly limited to the left-hemisphere structures, and even this involvement has met with substantive criticism (Crosson, 1992; Nadeau & Crosson, 1992). Indeed, the

low levels of activity seen in these right-hemisphere structures during the semantic condition would account for the asymmetry favoring the left lenticular region during the semantic task. It appears that these two findings are most readily attributed to an unknown factor which remained uncontrolled in the study or to expected error variance.

Another surprising finding was the lack of significant correlation between regions theoretically implicated in language. When reported, these correlations are usually quite high, although there is disagreement about the nature of the correlation between anterior and posterior regions (Bartlett et al., 1987; Frith et al., 1991). A difference between the current study and the correlations reported elsewhere is the nature of the cognitive states that were considered together. In other studies, correlations included values taken from rest, non-generative, and generative language tasks. Thus, the variability of the data may well have been much greater than in a paradigm such as the current one which compares three relatively complex generative language tasks. The effect of comparing between three relatively high level tasks may be analogous to "controlling for" a large number of processes subsumed by the functions being explored and the paradigm through which this exploration takes place. For instance, in this study, all of the steps involved in reading single words and generating responses nonvocally were common to all three tasks. This was done in an attempt to experimentally control for the patterns of neural behavior inherent to these steps. If one may assume that the generation of language is subserved by a relatively integrated network of subsystems, then the range across which this network has to function is dramatically reduced in the current methodology as compared to studies which compare tasks with no explicit language demand whatsoever to the generation or high-level comprehension of language. While this experimental control is desirable in terms of being able to interpret results, it has ramifications which should be considered. Statistically, this resulting loss of variability in the data may make correlations smaller. Thus, it may be that the more similar the cognitive activation tasks, the more difficult it will be to detect significant correlations between regions which preferentially handle different components of a complex cognitive activity.

Results were somewhat mixed when examining the within-task data. As predicted, there was a consistent asymmetry in the left frontal operculum in each task. The predicted asymmetry of

Wernicke's area in during the semantic task was also observed. There were a number of asymmetries which were not explicitly predicted as well. A consistent asymmetry was found in the inferior temporo-occipital association cortex (around Brodmann's area 37). The left hemisphere was significantly more active than its right hemisphere homologue during each task. As discussed in the literature review, this region is extensively interconnected with both visual association cortex and angular gyrus. The integrity of this region appears to be important for both semantic processes and reading, as well as other forms of visual analysis. While previous functional neuroimaging findings certainly suggested that this region would become more active during a reading task, the consistent asymmetry presents a couple of possibilities as to functional significance. First, in line with a hypothesis proposed by Wise and colleagues (1991) for the posterior superior temporal gyrus, it may be that Brodmann's area 37 represents some sort of "fundamental language" area which becomes significantly activated across all language tasks due to PDP mechanisms, the assumption being that perception of any linguistic stimulus initiates neural processes meant to derive meaning from the stimulus (e.g. emergent identification of lexical and semantic properties of the stimulus). A more likely explanation, however, is that this area becomes significantly activated during tasks which demand the orthographic processing of word-like figures. This explanation is clearly consistent with findings from both Petersen et al. (1989, 1990) and Marrett et al. (1992). The former group of authors found a significant response in an area that they refer to as "lateral extrastriate" whenever subjects were called to respond to "word-like figures," from strings of false fonts to real words (Petersen et al., 1990). When one examines the data presented in the article, however, the identified activation is extremely close to the posterior temporo-occipital association area, and limitations in the localization methodology certainly allow for a "near-miss" in identification of a locus of activity in these images. This activation was found to be approximately 30% greater on the left than on the right (Petersen et al., 1989). Marrett et al. (1992), using PET scans referenced to individual MR scans, also identified the dominant hemisphere temporo-occipital region as becoming significantly activated in activation conditions requiring processing of single visually-presented words. Thus, what one is most likely

observing in this region is increased input into a region important in the orthographic processing of visual word forms.

The asymmetries shown in the angular gyrus also show an interesting pattern. During the nonword rhyming task, the left angular gyrus was significantly more active than its right-hemisphere homologue. This asymmetry was significant only during the nonword rhyming task. This task was designed to be distinguishable from the others for its emphasis on grapheme-to-phoneme conversion independent of lexical and semantic processing. Informal debriefing of the subjects suggested that it was often "difficult to not come up with real words" during this task; as this difficulty was not assessed formally, the degree to which the task was performed independent of lexical processing remains unclear. As mentioned earlier, the angular gyrus has been identified as central in the process of understanding written language (Friedman & Albert, 1985). Thus, one possible interpretation of this asymmetry is that this region is important not only to normal reading but also to the process of grapheme-to-phoneme conversion. This interpretation would appear to be contradicted, however, by data suggesting that the angular gyrus region may be preferentially suited to the process of reading real words, while a more inferior pathway between visual association cortex and Wernicke's area may mediate grapheme-to-phoneme conversion (Rapcsak et al., 1987). Alternatively, the region may be playing a role in lexical processes. Notably, subjects consistently reported that it was difficult to inhibit the production of rhyming *real* words during the performance of this task. As "activation" in these scans does not distinguish between excitatory and inhibitory activity at the synaptic level, it may be that the observed asymmetry is reflective of increased *inhibition* of this region on the left relative to the right. The current paradigm does not allow the disentangling of these possibilities, however, so firm conclusions will have to await further studies.

Finally, a notable "non-finding" was the lack of significant asymmetry in dorsolateral prefrontal cortex. As mentioned previously, this finding had been extremely consistent across studies from many labs using equipment of varying spatial and temporal resolutions, so the absence of this asymmetry is puzzling. It may be that the dorsolateral prefrontal response is so intimately tied in with novelty of task that the practice the subjects received before the stimulation tasks in this study

attenuated the response in this area to some degree. Such a dynamic is supported both by Raichle's (1991) report of practice effects as well as theoretical accounts of the functions of the dorsolateral prefrontal cortex (Damasio, 1985; Stuss & Benson, 1986).

<u>Conclusions</u>

At its most basic level, then, it is felt that this study gives further support to a number of previously reported findings. The significant asymmetry in Brodmann's convexity area 37 during word form processing was replicated, and the suggestion that practice can affect both the magnitude and pattern of rCBF received additional support as well. Likewise, the consistent involvement of the left frontal opercular region in normal generative language tasks received further support. Although the aphasia literature suggests that the function of Broca's area in and of itself is neither necessary nor sufficient for effective generation of language (Alexander et al., 1990; Nadeau, 1988), it is evident from the functional neuroimaging literature that the synaptic activity in this region consistently increases when the generation of language is required.

This study also lends support to the importance of the dominant posterior superior temporal cortex in lexical-semantic processing. It is impossible to differentiate the two components of this processing on the basis of the results of this study, since the semantic association condition required the most processing of novel, meaningful stimuli as well as generation of lexical-semantic responses. Dissociation of the two components is clouded also by the consistent asymmetry of Brodmann's area 37, since this the region most typically implicated in syndromes in which semantic function is impaired, such as TCSA.

Finally, the findings raise interesting questions about the role of the angular gyrus during tasks that place a premium on grapheme-to-phoneme conversion and lexical processing (the latter required to produce a nonword). The presence of regional activation or inhibition may be conceptually supported on a post-hoc basis, but further empirical data are needed before firm conclusions may be drawn.

Directions for Future Research

At a general level, investigators will have to address a number of fundamental issues impacting on the interpretability of functional neuroimaging results in normals. At a basic neuroscience level, much work is needed in the further delineation of exactly what events are observable with functional neuroimaging techniques. Since it is now apparent that the changes one observes in comparing these scans is occurring at the synaptic level, the next step is to find out exactly what processes are occurring at the synaptic level. An important question to address is the ratio of interregional to intraregional synaptic activity across the different regions of the brain. This information undoubtedly has profound impact on the conclusions that can be drawn based on functional neuroimaging studies, but as yet it is simply not available. Furthermore, it will become increasingly important to explore how time affects the various measures that are being held out as indices of brain function. Questions about how the temporal resolution of particular scanning techniques impinge on the findings from different labs remain unanswered, and to date no one has reported findings in which the stimulation task and data analysis algorithm were held constant while the temporal resolution of the technique was varied. Likewise, the possibility that methodological variations as simple as changing the rate of stimulus presentation can profoundly affect the pattern of rCBF merits further investigation (Raichle, 1991).

The findings of this study also bring to light a number of issues that merit further investigation. In order to tease out the components of activation that are tied most strongly to stimulatory modality vs. language processing per se, it will be important to conduct studies which use different modes of stimulation within the same subjects. It would also be interesting to see if the hypothesis concerning the lack of significant anterior-posterior language region correlation could be confirmed by exploring correlations in studies that mix generative and non-generative conditions in the same subject group. If the logic presented in this paper is correct, one would predict that the correlations across generativity requirements would be greater than those within conditions in which the generativity requirement did not vary. In addition, the respective roles played by the left posterior superior temporal gyrus and the left inferior lateral prefrontal cortex in the comprehension of language

require more investigation, as findings between laboratories are clearly contradictory, both across functional neuroimaging studies and in comparing the functional neuroimaging data to the lesion literature. The data presented by this study, as well as those presented by Wise and colleagues (1991), appear to be most consistent with predictions that would be made based on the aphasia and neuroanatomical literature. The source of the discrepancy concerning the inferior lateral prefrontal region has yet to be fully uncovered.

Imagery and Concreteness of Verbs

Verbs differ in their capacity to arouse mental images of events or actions. Some words arouse a sensory experience, such as a mental picture or sound, very quickly and easily, whereas others may do so only with difficulty (i.e., after a long delay) or not at all. The purpose of this experiment is to rate a list of words as to the ease or difficulty with which they arouse mental images. Any word which, in your estimation, arouses a mental image (i.e., a mental picture, or sound, or other sensory experience) very quickly and easily should be given a *high imagery* rating; any word that arouses a mental image with difficulty or not at all should be given a *low imagery* rating. Think of the words "hit" and "is." Hit would probably arouse an image relatively easily and would be rated as high imagery; is would be rated as low imagery. Since the words tend to make you think of other words as associates, e.g., hit-slap, it is important that you note only the ease of getting a mental image of an object or an event to the word.

Your ratings will be made on a seven-point scale, where *one* is the low imagery end of the scale and *seven* is the high imagery end of the scale. Make your rating by filling in the number from 1 to 7 that best indicates your judgement of the ease or difficulty with which the word arouses imagery. The words that arouse mental images most readily for you should be given a rating of 7; words that arouse images with the greatest difficulty or not at all should be rated 1; words that are intermediate in ease or difficulty of imagery, of course, should be rated appropriately between the two extremes. *Feel free to use the entire range of numbers*, from 1 to 7; at the same time, don't be concerned about how often you use a particular number *as long as it is your true judgement*. Work fairly quickly but do not be careless in your ratings.

Another purpose of this study is to examine the "concreteness" of verbs. Verbs may refer to actions, experiences, or states of being that can be seen, heard, felt, smelled, or tasted or to more abstract concepts that cannot be experienced by our senses. One of the purposes of this experiment is to rate the list of verbs with respect to "concreteness" in terms of sense-experience. Any word that refers to easily quantified actions or experiences should receive a high concreteness rating; any word that refers to an abstract concept that cannot be experienced by the senses should receive a low concreteness rating. Think of the words "smash" and "evolve." "Smash" can be experienced by our senses and therefore should be rated as high concrete; "evolve" cannot be experienced by the senses as such and therefore should be rated as low concrete. Ratings are again on a seven point scale, with a rating of 1 denoting least concrete and 7 most concrete.

If necessary, refer back to these instructions when rating the words on the following pages.

APPENDIX B
RATINGS OF THE IMAGEABILITY AND CONCRETENESS OF 246 VERBS

	Imageability	Concreteness		Imageability	Concreteness
			park	5.538	4.615
run	6.692	6.308	celebrate	5.462	4.231
crash	6.615	6.538	flood	5.462	6.000
whip	6.615	6.615	lead	5.462	3.615
knock	6.538	6.000	melt	5.462	6.000
nail	6.462	6.231	steal	5.462	4.308
plow	6.385	5.308	argue	5.385	4.846
paint	6.308	5.615	mail	5.385	4.385
sweep	6.308	5.308	soak	5.385	6.077
sing	6.250	6.462	clean	5.308	4.538
point	6.231	5.000	terrify	5.308	4.769
spray	6.231	5.846	color	5.231	5.154
smoke	6.154	6.077	restrain	5.231	5.000
bloom	6.077	5.692	score	5.231	4.462
race	6.077	5.308	lean	5.154	4.538
whirl	6.077	5.769	shrink	5.154	5.231
shut	6.000	4.462	bet	5.077	3.308
stop	6.000	5.231	block	5.077	5.077
telephone	6.000	5.615	revolve	5.077	4.615
collapse	5.923	5.692	accelerate	5.000	4.462
embrace	5.923	5.769	announce	5.000	3.769
flash	5.923	5.231	compress	5.000	4.615
lift	5.923	5.846	record	5.000	4.154
rise	5.923	5.538	confront	4.846	4.000
weave	5.923	5.000	release	4.846	4.154
plant	5.846	5.308	warm	4.846	5.231
plunge	5.846	6.077	compose	4.835	2.769
press	5.846	5.846	charge	4.769	3.846
sigh	5.846	5.231	descend	4.769	4.385
shine	5.769	4.923	pile	4.769	4.615
study	5.769	4.000	complain	4.692	3.692
tumble	5.769	5.538	cripple	4.692	5.154
brush	5.692	5.692	shed	4.692	4.385
thrust	5.692	5.385	unload	4.692	4.154
tie	5.692	4.692	ask	4.615	3.615
vote	5.692	4.538	chill	4.615	5.231
arrest	5.615	4.462	excite	4.615	3.615
call	5.615	4.846	propose	4.615	3.000
slip	5.615	5.231	thank	4.615	3.692
spin	5.615	5.615	trail	4.615	3.308
unlock	5.615	4.385	harass	4.538	3.385
water	5.615	4.923	lower	4.538	3.615
rain	5.538	5.692	tire	4.538	4.615
scare	5.538	5.154	campaign	4.462	2.846
shock	5.538	6.154	observe	4.462	4.000
sprawl	5.538	5.231	place	4.462	3.846
spring	5.538	5.538	proclaim	4.462	3.538

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	Imageability	Concreteness		Imageability	Concreteness
shorten	4.462	3.769	advance	3.462	3.000
alert	4.385	3.154	cure	3.462	2.846
award	4.385	3.308	exhaust	3.462	4.000
connect	4.385	3.538	form	3.462	2.615
escort	4.385	3.308	furnish	3.462	2.923
dominate	4.308	3.000	isolate	3.462	2.692
welcome	4.308	3.000	traverse	3.462	3.231
assemble	4.231	3.000	despise	3.385	2.769
challenge	4.231	2.692	retire	3.385	2.692
ignore	4.231	2.692	hesitate	3.308	2.462
love	4.231	4.385	neglect	3.308	3.154
discover	4.154	2.846	notify	3.308	2.385
emerge	4.154	3.308	preside	3.308	2.077
handle	4.154	4.077	program	3.308	2.615
post	4.154	3.462	compile	3.231	2.154
seek	4.154	3.154	deny	3.231	2.308
display	4.077	3.846	promote	3.231	2.308
make	4.077	3.000	differ	3.154	2.231
pick	4.077	3.769	disturb	3.154	3.385
protect	4.077	2.462	encounter	3.154	2.846
slow	4.077	4.000	end	3.154	2.538
smooth	4.077	4.923	progress	3.154	3.077
think	4.077	2.769	reproduce	3.154	3.615
arouse	4.000	3.846	alter	3.154	2.308
choose	4.000	2.231	delegate	3.077	1.846
revive	4.000	2.769	reside	3.077	2.615
arrange	3.923	3.846	settle	3.077	3.231
board	3.923	3.154	suggest	3.077	2.385
convict	3.923	1.692	cancel	3.000	2.462
invite	3.923	2.615	claim	3.000	1.923
spoil	3.923	3.615	decline	3.000	2.615
warn	3.923	3.231	disrupt	3.000	3.077
add	3.846	2.385	motivate	3.000	3.077
contact	3.846	3.077	recover	3.000	2.615
couple	3.846	3.538	risk	2.962	2.154
detach	3.846	4.000	complete	2.923	1.769
encourage	3.846	2.769	employ	2.923	1.692
root	3.846	3.231	wish	2.923	1.769
avoid	3.769	2.077	affirm	2.846	2.000
persuade	3.769	2.231	dislike	2.846	2.615
visit	3.769	3.308	excuse	2.846	1.615
assist	3.692	2.462	reserve	2.846	2.000
clear	3.692	3.000	found	2.769	2.154
finish	3.692	2.462	keep	2.769	1.769
invent	3.692	2.615	restore	2.769	2.231
object	3.692	2.923	appreciate	2.692	1.769
blame	3.615	2.231	decrease	2.692	2.835
create	3.615	2.231	devote	2.692	1.615
denounce	3.615	2.308	locate	2.692	2.077
desert	3.615	2.692	adjoin	2.615	2.846
link	3.615	3.077	interpret	2.615	2.231
return	3.615	2.769	manage	2.615	2.000
compare	3.538	2.077	possess	2.615	1.692
disclose	3.538	2.462	single	2.615	1.692
pace	3.538	3.846	speculate	2.615	2.077
sport	3.538	3.000			

	Imageability	Concreteness
submit	2.615	2.462
uphold	2.615	2.231
augment	2.538	2.077
coordinate	2.538	2.077
emphasize	2.538	1.538
renew	2.538	2.000
sanction	2.538	2.077
consolidate	2.462	1.615
detail	2.462	2.000
determine	2.462	1.538
issue	2.462	1.769
belong	2.385	1.769
consider	2.385	1.615
engineer	2.385	1.846
evolve	2.385	1.846
realize	2.385	1.769
represent	2.385	2.385
convert	2.308	1.462
even	2.308	2.154
credit	2.231	1.846
continue	2.154	1.615
know	2.154	2.000
maintain	2.154	2.000
persist	2.154	1.769
prefer	2.154	1.769
situate	2.154	2.154
supplement	2.154	1.846
involve	2.077	1.538
regard	2.077	1.692
allege	2.000	1.462
characterize	2.000	1.615
engender	2.000	1.538
adapt	1.923	2.000
afford	1.769	1.615
transcend	1.769	1.462
forego	1.692	1.462
mean	1.692	2.077
happen	1.462	1.462
let	1.462	1.462
generalize	1.385	1.615
range	1.385	1.231

Rhyming Nonword Generation Task

In this task, we will be using nonwords, such as these (SHOW EXAMPLE SLIDE — trewin bule stets temeing blucip). For each nonword, you need to come up with a rhyming nonword. So, for instance, for the first nonword, you could say glewin or flewin or any other rhyming nonword. For the second word you could say hule or nule, etc. There are only three rules: first, you can't begin any of the words with the z sound; second, you can't begin all the words with the same sound; and third, the nonwords you come up with have to be nonwords. So, for instance, for hule, you couldn't say mule or fool or duel. You don't need to read the nonwords aloud: instead, just say the rhyming nonwords you come up with. Also, once we have gone through a few sets of nonwords make sure you have the hang of things, try not to say anything during the task other than the nonwords.

You'll be given around ten seconds to get through all the nonwords on each card card. At that point, the screen will go blank for a couple of seconds, and five new nonwords will appear. Try to work at a fairly rapid pace, and don't worry if you aren't able to finish a few cards. That's normal for the amount of time we give. Do you have any questions?

Semantic Association Task

In this task, you will see a list of five words on the screen (SHOW EXAMPLE), and your job will be to come up with a word associated with each one. Each associated word should be a word that most people would agree is clearly associated with the word on the screen. So, for instance, if you saw the word winter, you could say spring or season or snow, but you couldn't say something like football or something

related to a personal association. You don't need to say the words on the screen: just say the associated words you come up with. Also, once we have gone through a few sets of words to make sure you have the hang of things, try not to say anything during the task other than the associated words.

You will be given about ten seconds to come up with the five words. At that point, the screen will go blank for a couple of seconds, and five new words will appear. Try to work at a fairly rapid pace, and don't worry if you aren't able to finish a few cards. That's normal for the amount of time we give. Do you have any questions?

Syntactic Generation Task

In this task, you are going to be making some sentences. First, though, I'll go through and show you the types of sentences that you will need to make. On each card (or each screen), you will see five words. The first two will tell you what kind of sentence to make, and the last three will be the words around which you form the sentence.

(SHOW EXAMPLE) If the last three words are man, box, and lift, an obvious sentence you might make is "The man lifted the box." An obvious question you might make is "Did the man lift the box?" These types of sentences are called active structures, and they are the types most people use the most frequently. For this task, though, we are going to use two other types of structures. The first one is called the passive structure. Using this kind of structure for man, box, and lift, you would say "The box was lifted by the man." As a passive question, you could say "Was the box lifted by the man?" In looking at both of these sentences, you'll notice an easy way to remember the passive structures, in that they ALWAYS use the word BY. So, to use another example, (SHOW EXAMPLE 2) with the words shirt, man, and wrinkle, a passive statement would be "The shirt was wrinkled by the man," while a passive question would be "Was the shirt wrinkled by the man?" Again, you can see that every passive has the word BY in it. Do you have any questions so far? OK, now you try one. (SHOW EXAMPLE 3) With the words smash, computer, and student, what would be the passive statement be? (CORRECT IF WRONG) How about the passive question? (CORRECT IF WRONG) We'll try some more of these in a minute.

The other structure we'll be using is the cleft-object structure (SHOW EXAMPLE 1). With the words man, box, and lift, a cleft-object sentence would would like this: "It was the box that the man lifted." A cleft object question would go like this: "Was it the box that the man lifted?" An easy way to remember the cleft-object structure is that the verb is ALWAYS the LAST word in the sentence. So, for instance, (SHOW EXAMPLE 2), the cleft object statement here would be "It was the shirt that the man wrinkled," while the cleft-object question would be "Was it the shirt that the man wrinkled?" Do you have any questions so far? OK, now you try one. (SHOW EXAMPLE 3). With these words, what would the cleft-object statement be? (CORRECT IF WRONG) How about the cleft-object question? (CORRECT IF WRONG)

I need to mention a couple more things, and then I'll give you some more sentences to practice on. First, as I mentioned earlier, on each screen, you will see five words. The bottom three will be the ones you make the sentence out of, like the examples you have already seen. On the first line, you'll see either "passive" or "cleft-object", and on the second line, you will see either "statement" or "question"; in other words, the top two lines will tell you what to do with the bottom three lines. Also, once we have gone through a few sets of words to make sure you have the hang of things, try not to say anything during the task other than the sentences you come up with.

You will be given about ten seconds to come up with the five words. At that point, the screen will go blank for a couple of seconds, and five new words will appear. Try to work at a fairly rapid pace, and don't worry if you aren't able to finish a few cards. That's normal for the amount of time we give. Do you have any questions?

INSTRUCTIONS TO EXPERIMENTER AND SUBJECT FOR MAIN STUDY COGNITIVE
STIMULATION

Instructions for Rhyming Nonword Generation Task

In this task, we will be using nonwords, such as these (HIT ⌘-8. ONCE IN PSYCHLAB, HIT
⌘-7, SELECT PHONOLOGY TRAIN. HIT ⌘-0; HIT RETURN). For each nonword, you need to come
up with a rhyming nonword. So, for instance, for the first nonword, you could say glewin or flewin or any
other rhyming nonword. For the second word you could say hule or nule, etc. There are only three rules:
first, you can't begin the words with the z sound; so, for instance, you couldn't go down this set of words
and say zewin, zule, zets, zemeing, zlucip. Second, you can't begin all the words with the same sound; and
third, the nonwords you come up with have to be nonwords. So, for instance, for bule, you couldn't say
mule or fool or duel. You don't need to read the nonwords aloud: instead, just say the rhyming nonwords
you come up with. Any pronunciation of the word that you come up with is fine, so don't worry about
mispronunciations. Also, once we have gone through a few sets of nonwords to make sure you have the
hang of things, try not to say anything during the task other than the nonwords. Go ahead and try this set.
When you're done with this set, hit the space bar to get the next set.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE
RESULTS

OK. Now, during the rest of the afternoon, there will be a time limit for each set of words. You'll
be given a little more than 8 seconds to get through as many of the nonwords in each set as you can. You
probably won't finish all of the sets, because we intentionally made the interval for each set so that you

would be doing the task for the entire duration of the experiment. So, if you don't finish a set, don't worry, because chances are that not many other people will either. What I'm going to do now is show you approximately how much time you'll have to work on each set. Go ahead and try to come up with as many nonwords as you can.

HIT ⌘-Q, HIT ⌘-9, HIT ⌘-7, SELECT PHONOLOGY TRAIN II. HIT ⌘-0 AND THEN RETURN TO BEGIN THE TASK.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE RESULTS

PATIENT GOES FROM MONITOR ROOM TO SPECT ROOM

OK. Now we are going to begin the part of the experiment where you receive the injection. However, we're also going to give you a chance to earn a little extra money. One of the main things we are interested in is how silent practice affects how quickly you can come up with rhyming nonwords. Based on previous research, we suspect that silent practice increases performance, but only if the practice is done for about eight minutes and the person focuses on it for the entire time. Here's where the extra money comes in. Some of the nonword sets that you see during the silent practice we will administer again after the practice. If your performance is better on these word sets is better than the average of people coming up with rhyming nonwords to nonwords that they have never seen before, we'll pay you an extra ten dollars at the end of the day today. We'll be able to look at the data while you're in the scanner to see how you do. If you concentrate on the silent practice for the whole time and you work as quickly as you can on the words sets we repeat, this improvement should happen automatically. Do you have any questions?

OK, then we can go ahead and start the silent practice task. First, though, we are going to give you a little practice doing the task silently. What we want you to do is come up with rhyming nonwords

just like you have been doing, only this time say them to yourself in your head rather than saying them out loud. During this task, try not to make any sounds at all or move your mouth or throat in any way like you might do if you were saying the nonwords out loud. It's also important that you remain very still in general, so go ahead and find a position you'll be comfortable in for the next ten minutes or so. (WAIT FOR ANY POSITION CHANGE). OK, I'm going to show you a few sets of nonwords. Try to do them to yourself.

HIT F9, SELECT FINAL PHONOLOGY TRAIN. HIT F12 AND THEN RETURN TO BEGIN THE TASK.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE RESULTS

How did you do? (WAIT) Good, now we're ready to start with the practice. Again, this set is meant to give you an opportunity to practice the nonwords that you will be tested on after you complete the practice. It's important that you stay focused on the practice to maximize your chances of getting the extra money, since the nonwords that you'll see in the next part will be from random places in the silent practice set. Remember, after you have done the task for a little bit, Morris will inject the technetium, so just try to keep working on the task the whole time. Once you start, we'll be standing behind you, and we won't be able to answer any questions. Try not to talk to yourself at all other than saying the nonwords you come up with silently to yourself. Do you have any questions?

HIT F9, SELECT PHONOLOGY TASK. HIT F12 AND RETURN TO BEGIN.

AFTER 90 SECONDS, SIGNAL MORRIS TO BEGIN THE INJECTION.

DURING STIMULATION, MORRIS AND EXPERIMENTERS REMAIN QUIET BEHIND SUBJECT.

UPON COMPLETION, PATIENT MOVES FROM SPECT ROOM TO MONITOR ROOM.

TURN MICROPHONE ON; ATTACH TO SHIRT VIA SAFETY PIN

OK, now for the last task for the day. As we said, this set will consist of 30 sets of 5 nonwords that you saw during the silent practice, and you need to try your best to complete the nonwords as quickly as you can. If you focused on the silent practice, you shouldn't have any problem answering more quickly than average, but you'll still need to work as quickly as you can. Since you will have seen these nonword sets before, you may recognize some of them and remember the rhyme you came up with during the practice. If you do, go ahead and use it again. Remember, this is a test of speed, not creativity. Try to get through each set as quickly as you can. Do you have any questions?

PRESS RECORD AND PLAY SIMULTANEOUSLY ON TAPE RECORDER TO BEGIN TAPING;
SAY "SUBJECT #? -- PHONOLOGY"

HIT -7, SELECT PHONOLOGY TEST. HIT -0 AND RETURN TO BEGIN.

RECORD THE NUMBER OF RESPONSES PER SET OF STIMULI.

OK, now we'll let Morris get you set up in the scanner (OR GO TO THE MR LAB, AS APPLICABLE). While you're in the scanner, I'll compare your performances to see if you improved, so I'll know when you get out what the outcome was.

FAST FORWARD TAPE FOR A COUPLE OF SECONDS

<u>Instructions for Semantic Association Task</u>

In this task, you will see a list of five words on the screen (HIT ⌘-8. ONCE IN PSYCHLAB, HIT ⌘-7, SELECT PHONOLOGY TRAIN. HIT ⌘-6; HIT RETURN), and your job will be to come up with a word associated with each one. Each associated word should be a word that most people would agree is clearly associated with the word on the screen. So, for instance, if you saw the word winter, you could say spring or season or snow, but you couldn't say something like football or something related to a personal association. You don't need to say the words on the screen: just say the associated words you come up with. Also, once we have gone through a few sets of words to make sure you have the hang of things, try not to say anything during the task other than the associated words. Go ahead and try this set. When you're done with this set, hit the space bar to get the next set.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE RESULTS

OK. Now, during the rest of the afternoon, there will be a time limit for each set of words. You'll be given a little more than 8 seconds to get through as many of the words in each set as you can. You probably won't finish all of the sets, because we intentionally made the interval for each set so that you would be doing the task for the entire duration of the experiment. So, if you don't finish a set, don't worry, because chances are that not many other people will either. What I'm going to do now is show you approximately how much time you'll have to work on each set. Go ahead and try to come up with as many words as you can.

HIT ⌘-Q, HIT ⌘-9, HIT ⌘-7, SELECT SEMANTIC TRAIN II. HIT ⌘-0 AND THEN RETURN TO BEGIN THE TASK.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE
RESULTS

PATIENT GOES FROM MONITOR ROOM TO SPECT ROOM

OK. Now we are going to begin the part of the experiment where you receive the injection.
However, we're also going to give you a chance to earn a little extra money. One of the main things we are
interested in is how silent practice affects how quickly you can come up with clearly associated words.
Based on previous research, we suspect that silent practice increases performance, but only if the practice is
done for about eight minutes and the person focuses on it for the entire time. Here's where the extra money
comes in. Some of the word sets that you see during the silent practice we will administer again after the
practice. If your performance is better on these word sets is better than the average of people coming up
with words associated with words that they have never seen before, we'll pay you an extra ten dollars at the
end of the day today. We'll be able to look at the data while you're in the scanner to see how you do. If you
concentrate on the silent practice for the whole time and you work as quickly as you can on the words sets
we repeat, this improvement should happen automatically. Do you have any questions?

OK, then we can go ahead and start the silent practice task. First, though, we are going to give
you a little practice doing the task silently. What we want you to do is come up with associated words just
like you have been doing, only this time say them to yourself in your head rather than saying them out loud.
During this task, try not to make any sounds at all or move your mouth or throat in any way like you might
do if you were saying the words out loud. It's also important that you remain very still in general, so go
ahead and find a position you'll be comfortable in for the next ten minutes or so. (WAIT FOR ANY
POSITION CHANGE). OK, I'm going to show you a few sets of words. Try to do them to yourself.

HIT F9, SELECT FINAL SEMANTIC TRAIN. HIT F12 AND THEN RETURN TO BEGIN THE
TASK.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE
RESULTS

How did you do? (WAIT) Good, now we're ready to start with the practice. Again, this set is
meant to give you an opportunity to practice the words that you will be tested on after you complete the
practice. It's important that you stay focused on the practice to maximize your chances of getting the extra
money, since the words that you'll see in the next part will be from random places in the silent practice set.
Remember, after you have done the task for a little bit, Morris will inject the technetium, so just try to keep
working on the task the whole time. Once you start, we'll be standing behind you, and we won't be able to
answer any questions. Try not to talk to yourself at all other than saying the words you come up with
silently to yourself. Do you have any questions?

HIT F9, SELECT SEMANTIC TASK. HIT F12 AND RETURN TO BEGIN.

AFTER 90 SECONDS, SIGNAL MORRIS TO BEGIN THE INJECTION.

DURING STIMULATION, MORRIS AND EXPERIMENTERS REMAIN QUIET BEHIND
SUBJECT.

UPON COMPLETION, PATIENT MOVES FROM SPECT ROOM TO MONITOR ROOM.

TURN MICROPHONE ON; ATTACH TO SHIRT VIA SAFETY PIN

OK, now for the last task for the day. As we said, this set will consist of 30 sets of 5 words that
you saw during the silent practice, and you need to try your best to complete the words as quickly as you
can. If you focused on the silent practice, you shouldn't have any problem answering more quickly than

average, but you'll still need to work as quickly as you can. Since you will have seen these nonword sets before, you may recognize some of them and remember the word you came up with during the practice. If you do, go ahead and use it again. Remember, this is a test of speed, not creativity. Try to get through each set as quickly as you can. Do you have any questions?

PRESS RECORD AND PLAY SIMULTANEOUSLY ON TAPE RECORDER TO BEGIN TAPING:

SAY "SUBJECT #? -- SEMANTIC"

HIT ⬣-7, SELECT SEMANTIC TEST. HIT ⬣-0 AND RETURN TO BEGIN.

RECORD THE NUMBER OF RESPONSES PER SET OF STIMULI.

OK, now we'll let Morris get you set up in the scanner (OR GO TO THE MR LAB, AS APPLICABLE). While you're in the scanner, I'll compare your performances to see if you improved, so I'll know when you get out what the outcome was.

FAST FORWARD TAPE FOR A COUPLE SECONDS

Instructions for the Syntactic Structuring Task

In this task, you are going to be making some sentences. First, though, I'll go through and show you the types of sentences that you will need to make. On each set of words (or each screen), you will see five words. The first two will tell you what kind of sentence to make, and the last three will be the words around which you form the sentence.

(HIT ♣-8. ONCE IN PSYCHLAB, HIT ♣-7, SELECT SYNTAX TRAIN. HIT ♣-0; HIT RETURN) If the last three words were man, box, and lift, an obvious sentence you might make is "The man lifted the box." An obvious question you might make is "Did the man lift the box?" These types of sentences are called active sentences, and they are the types that people use the most frequently. For this task, though, we are going to use two other types of sentences. The first one is called the passive sentence. Using this kind of sentence for man, box, and lift, you would say "The box was lifted by the man." As a passive question, you could say "Was the box lifted by the man?" In listening to both of these sentences, you'll notice that an easy way to remember the passive sentences is that they ALWAYS use the word BY; so, to make this easier for you to remember, we'll call these BY sentences from here on out. To use another example, (HIT SPACE BAR) with the words shirt, man, and wrinkle, a BY statement would be "The shirt was wrinkled by the man," while a BY question would be "Was the shirt wrinkled by the man?" Do you have any questions so far? OK, now you try one. (HIT SPACE BAR) With the words smash, computer, and student, what would the BY statement be? (CORRECT IF WRONG). How about the BY question? (CORRECT IF WRONG). We'll try some more of these in a minute.

The other sentence we'll be using is the cleft-object sentence (HIT SPACE BAR). People use the cleft-object sentence to specify what they mean. For example, with the words man, box, and lift, a cleft-object sentence would look like this: "That was the box that the man lifted." A cleft object question would go like this: "Was that the box that the man lifted?" An easy way to remember the cleft-object sentence is that the verb is ALWAYS the LAST word in the sentence: so, to make this easier for you to remember, we'll call these sentences VERB-LAST sentences from here on out. Another way this sentence is different from the BY sentences is that the word "that" is ALWAYS the first word in the VERB-LAST

statements and ALWAYS the second word in the VERB-LAST questions that we will be using. In contrast, the word "that" is never one of the first two words in the BY statements and questions that we will be using. As another example (HIT SPACE BAR), the VERB-LAST statement here would be "That was the shirt that the man wrinkled," while the VERB-LAST question would be "Was that the shirt that the man wrinkled?" Do you have any questions so far? OK, now you try one. (HIT SPACE BAR). With these words, what would the VERB-LAST statement be? (CORRECT IF WRONG) How about the VERB-LAST question? (CORRECT IF WRONG)

I need to mention a couple more things, and then I'll give you some more sentences to practice on. First, as I mentioned earlier, you will see five words on each screen. The bottom three will be the ones you make the sentence out of, like the examples you have already seen. These won't be in any particular order, and you can change the form of the words in any way that you need to make the statement or question work. On the first line (POINT), you'll see either "BY" or "VERB-LAST", and on the second line (POINT), you will see either "STATEMENT" or "QUESTION"; in other words, the top two lines will tell you what to do with the bottom three lines. There won't be any trick questions: all of the sets that you see can be made into statements and questions. However, some of the words might be able to be used as a noun or a verb, like the word "watch" for example. You can look at your watch, or you could watch a football game. So, if a set of words doesn't seem to make sense, it might be that one of the words can be used another way. Finally, once we have gone through a few sets of words to make sure you have the hang of things, try not to say anything during the task other than the sentences you come up with. Now we're going to go through a few practice trials to make sure you have the hang of things. Go ahead and try this set. When you're done with this set, hit the space bar to get the next set.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE RESULTS

OK. Now, during the rest of the afternoon, there will be a time limit for each set of words. You'll be given a little more than 8 seconds to come up with each statement or question. You probably won't

finish all of the sets, because we intentionally made the interval for each set so that you would be doing the task for the entire duration of the experiment. So, if you don't finish a set, don't worry, because chances are that not many other people will either. What I'm going to do now is show you approximately how much time you'll have to work on each set. Go ahead and try to come up with as many statements or questions as you can.

HIT ⌘-Q, HIT ⌘-9, HIT ⌘-7, SELECT SYNTAX TRAIN II. HIT ⌘-0 AND THEN RETURN TO BEGIN THE TASK.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE RESULTS

PATIENT GOES FROM MONITOR ROOM TO SPECT ROOM

OK. Now we are going to begin the part of the experiment where you receive the injection. However, we're also going to give you a chance to earn a little extra money. One of the main things we are interested in is how silent practice affects how quickly you can come up with statements and questions. Based on previous research, we suspect that silent practice increases performance, but only if the practice is done for about eight minutes and the person focuses on it for the entire time. Here's where the extra money comes in. Some of the word sets that you see during the silent practice we will administer again after the practice. If your performance is better on these word sets is better than the average of people coming up with statements and questions with words that they have never seen before, we'll pay you an extra ten dollars at the end of the day today. We'll be able to look at the data while you're in the scanner to see how you do. If you concentrate on the silent practice for the whole time and you work as quickly as you can on the words sets we repeat, this improvement should happen automatically. Do you have any questions?

OK, then we can go ahead and start the silent practice task. First, though, we are going to give you a little practice doing the task silently. What we want you to do is come up with statements and questions just like you have been doing, only this time say them to yourself in your head rather than saying them out loud. During this task, try not to make any sounds at all or move your mouth or throat in any way like you might do if you were saying the words out loud. It's also important that you remain very still in general, so go ahead and find a position you'll be comfortable in for the next ten minutes or so. (WAIT FOR ANY POSITION CHANGE). OK, I'm going to show you a few sets of words. Try to do them to yourself.

HIT F9, SELECT FINAL SYNTAX TRAIN. HIT F12 AND THEN RETURN TO BEGIN THE TASK.

WHEN THE TASK IS OVER, HIT CANCEL IN BOTH WINDOWS THAT ASK TO SAVE RESULTS

How did you do? (WAIT) Good, now we're ready to start with the practice. Again, this set is meant to give you an opportunity to practice the words that you will be tested on after you complete the practice. It's important that you stay focused on the practice to maximize your chances of getting the extra money, since the words that you'll see in the next part will be from random places in the silent practice set. Remember, after you have done the task for a little bit, Morris will inject the technetium, so just try to keep working on the task the whole time. Once you start, we'll be standing behind you, and we won't be able to answer any questions. Try not to talk to yourself at all other than saying the statements and questions you come up with silently to yourself. Do you have any questions?

HIT F9, SELECT SYNTAX TASK. HIT F12 AND RETURN TO BEGIN.

AFTER 90 SECONDS, SIGNAL MORRIS TO BEGIN THE INJECTION.

DURING STIMULATION, MORRIS AND EXPERIMENTERS REMAIN QUIET BEHIND
SUBJECT.

UPON COMPLETION, PATIENT MOVES FROM SPECT ROOM TO MONITOR ROOM.

TURN MICROPHONE ON; ATTACH TO SHIRT VIA SAFETY PIN

OK, now for the last task for the day. As we said, this set will consist of 30 sets of 5 words that
you saw during the silent practice, and you need to try your best to complete the sentences and questions as
quickly as you can. If you focused on the silent practice, you shouldn't have any problem answering more
quickly than average, but you'll still need to work as quickly as you can. Since you will have seen these
word sets before, you may recognize some of them and remember the statement or question you came up
with during the practice. If you do, go ahead and use it again. Remember, this is a test of speed, not
creativity. Try to get through each set as quickly as you can. Do you have any questions?

PRESS RECORD AND PLAY SIMULTANEOUSLY ON TAPE RECORDER TO BEGIN TAPING:
SAY "SUBJECT #? -- SYNTAX"

HIT ♣-7, SELECT SYNTAX TEST. HIT ♣-0 AND RETURN TO BEGIN.

RECORD THE CORRECTNESS OF EACH RESPONSE.

OK, now we'll let Morris get you set up in the scanner (OR GO TO THE MR LAB, AS
APPLICABLE). While you're in the scanner, I'll compare your performances to see if you improved, so I'll
know when you get out what the outcome was.

FAST FORWARD TAPE FOR A COUPLE SECONDS

Stimuli for Nonword Rhyming Task

Training Stimuli

trewin buki stets temeing hlucip
serucs plus siks sal thilg
lilps salpbs ools niup bedi
vige kawl nophe gifth ubst
ginvir ogd soof zenici magelb
steris dese thilgnoc yenom gernuh
rafe stearure nairt cusk seeds
ruho mnal rilg thero esu
sendinks tagteuc thafer dworl nos
reipsi merraf thorber tars nilo
cusim woc nahd tenrain crubch
guh pnalt raneg tipy tac

Stimulation Stimuli

guilbind neaco teik lirg tarstel
nurvoert grof yoneh noom lade
velon tiphnk hanic wims malp
ryf rited nowq tudsent lulp
lestepoce foressorp flew mentarap mna
rea chend triew shurbed riccle
slerwof darg lilch nasit shurb
raih leaserc chape salgs eey
dilch hursh tulm sdrup sitrat
oolt culette sbif cbout loiserd
tudsy gandabe rasce volge samsage
reif stout plila brenaice regiuf
voncent dwara radmila slooch swon
sharas quirlers lilps riccus skruct
patzibe gaornam plpez klanteb tuds
toabails nilfs radape reateccela sewir
terlet murprut sharlmal foalbolt eawve
coshk paicun middoan ceuk seeds
krinsh sunh tewall clonuk nogs
tej gahn marf oosht taliposh
noam dynac cernad milf cbearet
sumic cuip toub ugt goaren
yenom rincep gontue stunes caunt
hirck therom parge deurh pamend
tunawl krush storec murd roich
traceleb thesw ild counneam seeps
sterrain nem eap phragophot glerag
eshd garnican leats pleogbe doulher
twon vimoe swah rawm surne
blevetage nowam mcalf reiig renish
fwol versobe presscin aim gins

Post-Test Stimuli

guilbind neaco teik lirg tarstel
velon tiphnk hanic wims malp
slerwof darg lilch nasit shurb
raih leaserc chape salgs eey
oolt culette sbif cbout loiserd
tudsy gandabe rasce volge samsage
voncent dwara radmila slooch swon
sharas quirlers lilps riccus skruct
noam dynac cernad milf cbearet
yenom rincep gontue stunes caunt
hirck therom parge deurh pamend
tunawl krush storec murd roich
twon vimoe swah rawm surne

reab dalbe moorb smalina oshe
ylf panst kilc ruhe shundab
tuboninals tuife elax pboletene werfols
flatine xof danh lanckece plis
pnalt kael rourp leddap
lednah cickoo yed lalc nishe
liad stinimer gwin fieth wolp
mokes salpg sencit leam struth
filt yek neque atc thoam
noil nairh yoh nopy coagett
suvternity nirg kawl nealc wol
teag rabotac teask sten daplaup
ractor calape gink ragon geabd
sterra tighn reet neccont tilqu
loroc rettash rotnesh dutla rowds
drunlan nairt myg geam keah
sarug fronroc pnait doof proapcha
ichli thilg sonte leyval daor
dray seehsad taych malb vasbe
drocer yarsp desh monel kooh
telrut kcar tac tasete tich
keal leewb nur tah poina
quernit verir plew pyppu gwins
acheth plas lord oryvi robreth
reathel trasccb nowlc tersis aiim
anaabs crenck rionacma dianin rhucch
cerd nagder niopt rollad bolck
wodwin kaath teap necbick shup
naywel kajtec roshew chestorra hlovellaylh
teln rnra gillave noic rac
prak kasbe geersant pallosce torcod
wronc scibuit lem tipch pellap
boollan pejp garcbe risht ote

bievetage nowam mealf retig remin
reah daibe moorb smalina oshe
tubontmals tulfe elax pholetene werfols
lednah cidceo yad lalc nishe
liad stimmer gwin ficeb wolp
mokes siday sencit team struth
noil nairb yoh nopy coagett
teag rabouc izask sten daphaup
ractor calape pink ragon geabd
loroc rettash rotnesh dutla rowds
dray sechsad tayth maib vashe
droccr yarup desh monel koob
keal lcewb nar tah poina
acheth plas lorl oryvi robreth
annaba crewk rionacma dinnin rhucch
prak kashe geersant pallosce xorcod
boollan peip garche risbt cte

Stimuli for Semantic Association Task

Training Stimuli

winter blue tests meeting public
connect fly exotic bandage rattle
apple suntan beard nest sandal
ocean ham valley mouth leather
pile stir walk inflate slap
quarter lemon gate guilt lips
circle yerd juice food shirt
necklace drum heart tool glass
book piano stone emerald steak
diamond garden yacht banana organ
ear tongue magazine university violin

Stimulation Stimuli

men kite convent letter award
duchess cat male sunset lion
shrink plant stop lead sing
church milk flame hospital paint
run bel release confront record
cake baby colonel smile mosquito
prince snow kitten choir lamp
trucks minister bodder football cottage
restrain flash call spin steal
aunt gin medal trumpet hermit
ask shatter cripple embrace soak
accelerate thrust chill announce tie
tractor teacher boy puppy miner
observe scrape weave collapse unload
gargle wreck shoot sweep roll
magician apartment hand horse uncle
hat novel balloon orange honey
arm frog sailboat tape reptile
priest nurse artist deer village
spin squirrel orchestra glove train
eat post charge spray study
drench lick spill wipe shovel

tug climb dye fry toast
elm cookie brick pipe kid
massage pour push rake startle
owl sugar lamb satin coin
school palace gown night telescope
acrobat parade photograph pastor game
shock plow love thank mail
music turtle child wheel building
puddle dial baptize applaud write
escort scare bake point park
captain sister lantern tiger down
dress key flowers button king
animals hatchet moon lower volleyball
shut drag topple hang race
pitch dampen touch shred sniff
ape pants insect ivory doughnut
chili wallet wing toe candy
approach swing terrify wash shake
woman blacksmith tree car shoe
peach river flute biscuit vegetable
kiss sever puncture repair slam
shower movie color farm sword
money pony doctor wife light
soldier telephone mother dancer wires
queen people hand cabin lawyer
highway window eye grape gym
lettuce road ring wheat jet
fox admiral badge seed cereal
ground soup estate smoke chicken
princess fire rabbit rain adult
blade professor friend girl sailor
overturn moan pile pull flood
knight hair anchor brother hood
limousine blanket president dollar bracelet
block bite shorten clean water
axle man indian camp broom
husband marshall nuns wolf circus
connect unlock excite shine whip
melt handle shed press harass
student brain walnut crown boat
crash warm lift dust brushed
bear town finger icecream team

Post-Test Stimuli

duchess cat male sunset lion
church milk flame hospital paint
run bel release confront record
aunt gin medal trumpet hermit
tractor teacher boy puppy miner
magician apartment hand horse uncle
eat post charge spray study
drench lick spill wipe shovel
massage pour push rake startle
school palace gown night telescope
shock plow love thank mail
dress key flowers button king
shut drag topple hang race
chili wallet wing toe candy

approach swing terrify wash shake
kiss sever puncture repair slam
shower movie color farm sword
soldier telephone mother dancer wires
queen people band cabin lawyer
highway window eye grape gym
princess fire rabbit rain adult
blade professor friend girl sailor
knight hair anchor brother bird
block bite shorten clean water
axle man indian camp broom
husband mushroom band wild circus
connect unlock excite shine whip
melt handle shed press harass
student brain walnut crown boat
crash warm lift dust brushed

<u>Stimuli for Syntactic Generation Task</u>

Training Stimuli

. . man box lift
. . shirt man wrinkle
. . smash computer student
. man box lift
. . shirt man wrinkle
. . smash computer student
verb-last statement girlfriend marry boyfriend
by statement caress mother child
verb-last question baker cook pie
by question boy walk dog
by statement battle fight soldier
verb-last question candy eat girl
verb-last statement music dancer love
by statement church give clothing
by statement police citizen phone
by question woman daughter dress
verb-last statement bug son puppy
by question family priest comfort
verb-last question kiss bride man
by statement button soldier press
verb-last question water shrink dress
by statement dust broom pile
by statement football team charge
verb-last statement monkey person train
by question band glove restrain
verb-last statement clown circus announce
by statement camp warm lantern
verb-last question town flood shower
by question fire building collapse

<u>Stimulation Stimuli</u>

verb-last statement tractor plow farm
verb-last question paint artist cottage
verb-last question lion whip man
by statement sing choir song

verb-last statement wife point finger
by question hermit plant tree
verb-last statement brother smile park
verb-last statement limousine uncle park
by statement pipe professor smoke
verb-last statement mail friend letter
by question blanket girl weave
by question husband movie terrify
verb-last statement record music orchestra
by question turtle rabbit race
by statement admiral anchor lower
by statement kite color boy
by question light elm block
verb-last statement teacher kid harass
verb-last statement observe sunset people
by question steal walnut squirrel
by statement bait cat shed
by statement flame melt icecream
by question chill snow village
by statement sweep lady cabin
verb-last question mother embrace child
by question lead band parade
verb-last statement milk cereal soak
by statement bear fox confront
by question bake woman cookie
verb-last question church minister clean
by statement lawyer estate handle
verb-last question eat bird seed
verb-last statement hospital doctor telephone
by statement queen magician shook
by question lift baby aunt
verb-last statement accelerate car brother
verb-last question horse call knight
verb-last statement game excite acrobat
by statement pony indian release
by question thank president princess
verb-last question bet money prince
by statement nurse love kitten
by question escort priest sister
verb-last question photograph post dancer
by statement unload men trucks
by statement shoe tie adult
by question award king medal
verb-last question pastor bite mosquito
verb-last statement boat sailor crash
verb-last question boulder train stop
by statement flowers sniff lamb
verb-last question run convent nuns
verb-last statement flash marshall badge
by question shine lamp miner
verb-last question sword soldier thrust
verb-last statement shatter brick window
by question wires connect sergeant
verb-last statement wheel spin axle
verb-last question tiger cripple deer
by statement colonel captain ask

by question shorten blade blacksmith
verb-last question drink baby milk

Post-Test Stimuli

verb-last statement tractor plow farm
verb-last question paint artist cottage
by statement sing choir song
verb-last statement limousine uncle park
by statement pipe professor smoke
by question blanket girl weave
verb-last statement record music orchestra
by statement kite color boy
by question steal walnut squirrel
by statement flame melt icecream
by question lead band parade
verb-last statement milk cereal soak
by statement bear fox confront
by question bake woman cookie
verb-last question church minister clean
verb-last question eat bird seed
verb-last statement game excite acrobat
by question thank president princess
verb-last question bet money prince
by question escort priest sister
verb-last question photograph post dancer
verb-last question boulder train stop
by statement flowers sniff lamb
verb-last statement flash marshall badge
by question shine lamp miner
verb-last question sword soldier thrust
by statement brushed duchess puppy
verb-last statement wheel spin axle
by question shorten blade blacksmith
verb-last question drink baby milk

CORRELATIONS BETWEEN ADJUSTED REGIONAL COUNTS AND EFFORT INDICES
(REACTION TIME TO NOVEL STIMULI AND SUBJECTIVE RATING OF DIFFICULTY) WITHIN
AND ACROSS CONDITIONS

	Across Tasks		Nonword Rhyming		Semantic Assoc.		Syntactic Gen.	
Region	RT-Novel	VAS Rating	RT-Novel	VAS Rating	RT-Novel	VAS Rating	RT-Novel	VAS Rating
Whole Brain	0.17	0.10	0.25	0.22	0.20	0.26	0.03	0.05
Striate	0.21	0.05	0.42	0.07	0.42	0.50	0.11	0.33
Frontal Operculum								
Left	0.26	0.15	0.17	0.13	0.10	0.15	0.11	0.29
Right	0.02	0.18	0.27	0.13	0.01	0.15	0.17	0.19
Dorsolateral Frontal(s.5)								
Left	0.23	0.22	0.08	0.11	0.34	0.40	0.05	0.17
Right	0.03	0.04	0.08	0.22	0.02	0.32	0.38	0.18
Dorsolateral Frontal(s.6)								
Left	0.03	0.20	0.20	0.12	0.04	0.86	0.39	0.00
Right	0.01	0.09	0.02	0.13	0.09	0.43	0.33	0.05
Inferior Frontal								
Left	0.20	0.15	0.22	0.10	0.07	0.20	0.04	0.19
Right	0.15	0.23	0.02	0.05	0.33	0.54	0.87	0.33
Motor Strip								
Left	0.02	0.03	0.16	0.13	0.30	0.37	0.04	0.11
Right	0.10	0.10	0.54	0.42	0.04	0.30	0.33	0.02
Sensory Strip								
Left	0.24	0.33	0.27	0.37	0.01	0.27	0.20	0.16
Right	0.01	0.08	0.12	0.31	0.30	0.44	0.27	0.01
Wernicke's Area								
Left	0.13	0.13	0.13	0.11	0.03	0.61	0.52	0.38
Right	0.14	0.27	0.45	0.38	0.12	0.11	0.34	0.17
Supramarginal Gyrus								
Left	0.21	0.20	0.20	0.15	0.38	0.48	0.28	0.52
Right	0.08	0.25	0.27	0.51	0.50	0.35	0.05	0.00
Angular Gyrus								
Left	0.49	0.02	0.57	0.14	0.41	0.68	0.61	0.09
Right	0.01	0.12	0.44	0.38	0.05	0.15	0.18	0.04
Temporo-Occipital								
Left	0.20	0.07	0.22	0.22	0.06	0.38	0.62	0.14
Right	0.15	0.01	0.10	0.39	0.29	0.06	0.32	0.17
Lenticular Nuclei								
Left	0.36	0.46	0.34	0.21	0.19	0.24	0.43	0.68
Right	0.56	0.40	0.53	0.20	0.11	0.19	0.32	0.46
Head of the Caudate								
Left	0.04	0.25	0.20	0.20	0.67	0.07	0.08	0.44
Right	0.12	0.17	0.16	0.26	0.46	0.16	0.33	0.32
Thalamus								
Left	0.20	0.17	0.59	0.19	0.17	0.22	0.17	0.22
Right	0.09	0.17	0.41	0.00	0.26	0.09	0.56	0.47

Adjusted Counts in Frontal Operculum by Task
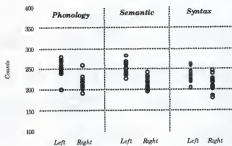
Adjusted Counts in Dorsolateral Prefrontal Region (s. 5) by Task
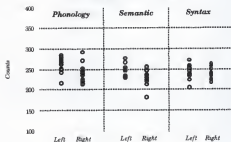
Adjusted Counts in Dorsolateral Prefrontal Region (s.6) by Task
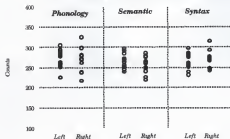
Adjusted Counts in Inferior Frontal Region by Task
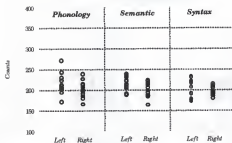
Adjusted Counts in Motor Cortex by Task
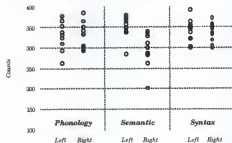
Adjusted Counts in Sensory Cortex by Task
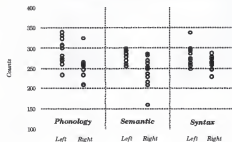
Adjusted Counts in Posterior Superior
Temporal Cortex by Task
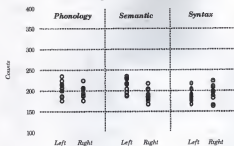
Adjusted Counts in Supermarginal Gyrus
by Task
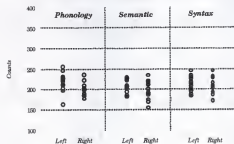
Adjusted Counts in Angular Gyrus
by Task
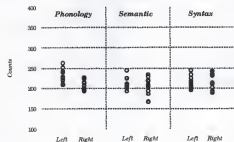
Adjusted Counts in Temporo-Occipital Association Cortex by Task
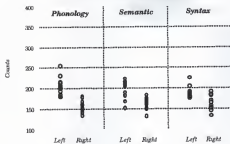
Adjusted Counts in Striate Cortex By Task
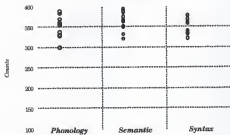
Adjusted Counts in Lenticular Nuclei by Task
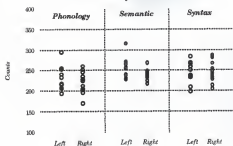
Adjusted Counts in Head of Caudate by Task
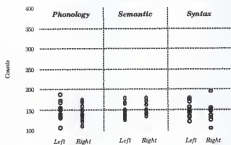
Average Counts in Thalamic Nuclei Across Tasks
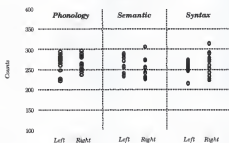
PARTIAL CORRELATIONS (CONTROLLING FOR GLOBAL COUNTS) BETWEEN REGIONS

PARTIAL CORRELATIONS

	LBROCA	LDF1	LDF2	LINFRONT	LMOTOR
LBROCA	1.000				
LDF1	0.643	1.000			
LDF2	0.453	0.803	1.000		
LINFRONT	0.556	0.259	-0.180	1.000	
LMOTOR	0.457	0.603	0.576	-0.055	1.000
LSENSORY	0.253	0.502	0.345	0.005	0.726
LWERNICK	0.473	0.243	0.490	0.130	0.140
LSPRMRG	0.302	0.020	-0.180	0.173	0.395
LANGGYR	0.247	0.159	0.278	0.083	0.307
LOTP	0.081	0.148	0.314	-0.073	-0.380
LLNTNUC	-0.319	-0.545	-0.068	-0.455	-0.338
LCAUDNUC	-0.083	-0.466	-0.205	-0.096	-0.483
LTHAL	-0.043	0.007	0.399	-0.519	-0.182

	LSENSORY	LWERNICK	LSPRMRG	LANGGYR	LOTP
LSENSORY	1.000				
LWERNICK	0.028	1.000			
LSPRMRG	0.507	0.271	1.000		
LANGGYR	0.511	0.576	0.432	1.000	
LOTP	-0.496	0.418	-0.403	-0.238	1.000
LLNTNUC	-0.553	0.096	-0.537	-0.273	0.380
LCAUDNUC	-0.608	0.142	-0.366	-0.368	0.508
LTHAL	-0.533	0.297	-0.303	-0.303	0.538

	LLNTNUC	LCAUDNUC	LTHAL
LLNTNUC	1.000		
LCAUDNUC	0.848	1.000	
LTHAL	0.508	0.327	1.000

MATRIX OF PROBABILITIES

	LBROCA	LDF1	LDF2	LINFRONT	LMOTOR
LBROCA	0.000				
LDF1	0.024	0.000			
LDF2	0.140	0.002	0.000		
LINFRONT	0.060	0.416	0.577	0.000	
LMOTOR	0.135	0.038	0.050	0.866	0.000
LSENSORY	0.428	0.096	0.273	0.989	0.007
LWERNICK	0.120	0.447	0.106	0.688	0.665
LSPRMRG	0.340	0.950	0.576	0.591	0.203
LANGGYR	0.440	0.621	0.381	0.798	0.332
LOTP	0.802	0.646	0.321	0.821	0.223
LLNTNUC	0.312	0.067	0.834	0.138	0.200
LCAUDNUC	0.798	0.127	0.522	0.767	0.112
LTHAL	0.894	0.982	0.199	0.084	0.572

MATRIX OF PROBABILITIES

	LSENSORY	LWERNICK	LSPRMRG	LANGGYR	LOTP
LSENSORY	0.000				
LWERNICK	0.931	0.000			
LSPRMRG	0.092	0.394	0.000		
LANGGYR	0.090	0.050	0.160	0.000	
LOTP	0.101	0.176	0.194	0.457	0.000
LLNTNUC	0.062	0.768	0.072	0.391	0.222
LCAUDNUC	0.036	0.661	0.242	0.239	0.092
LTHAL	0.075	0.349	0.220	0.338	0.071

	LLNTNUC	LCAUDNUC	LTHAL
LLNTNUC	0.000		
LCAUDNUC	0.000	0.000	
LTHAL	0.092	0.299	0.000

PARTIAL CORRELATIONS

	RBROCA	RDF1	RDF2	RINFRONT	RMOTOR
RBROCA	1.000				
RDF1	0.784	1.000			
RDF2	0.592	0.899	1.000		
RINFRONT	0.248	0.174	0.057	1.000	
RMOTOR	0.570	0.732	0.778	-0.298	1.000
RSENSORY	0.193	0.422	0.555	-0.057	0.422
RWERNICK	0.165	0.570	0.542	0.047	0.309
RSPRMRG	-0.328	0.129	0.377	-0.307	0.137
RANGGYR	0.113	0.389	0.415	0.026	0.128
ROTP	0.455	0.164	-0.073	-0.036	-0.024
RLNTNUC	-0.559	-0.621	-0.480	-0.328	-0.737
RCAUDNUC	-0.093	-0.316	-0.281	-0.141	-0.404
RTHAL	0.208	0.264	0.326	-0.442	0.261

	RSENSORY	RWERNICK	RSPRMRG	RANGGYR	ROTP
RSENSORY	1.000				
RWERNICK	0.544	1.000			
RSPRMRG	0.563	0.665	1.000		
RANGGYR	0.747	0.747	0.721	1.000	
ROTP	-0.174	-0.288	-0.195	0.105	1.000
RLNTNUC	-0.289	-0.020	-0.062	0.011	0.241
RCAUDNUC	-0.314	-0.034	-0.256	-0.053	0.617
RTHAL	0.076	-0.017	-0.165	-0.077	0.207

	RLNTNUC	RCAUDNUC	RTHAL
RLNTNUC	1.000		
RCAUDNUC	0.769	1.000	
RTHAL	0.039	0.391	1.000

MATRIX OF PROBABILITIES

	RBROCA	RDF1	RDF2	RINFRONT	RMOTOR
RBROCA	0.000				
RDF1	0.003	0.000			
RDF2	0.042	0.000	0.000		
RINFRONT	0.436	0.588	0.860	0.000	
RMOTOR	0.053	0.007	0.003	0.346	0.000
RSENSORY	0.549	0.173	0.061	0.861	0.172
RWERNICK	0.608	0.053	0.068	0.885	0.329
RSPRMRG	0.299	0.693	0.581	0.331	0.672
RANGGYR	0.726	0.211	0.180	0.937	0.692
ROTP	0.138	0.612	0.823	0.913	0.942
RLNTNUC	0.059	0.031	0.114	0.932	0.006
RCAUDNUC	0.774	0.317	0.376	0.662	0.193
RTHAL	0.517	0.407	0.301	0.150	0.413

MATRIX OF PROBABILITIES

	RSENSORY	RWERNICK	RSPRMRG	RANGGYR	ROTP
RSENSORY	0.000				
RWERNICK	0.068	0.000			
RSPRMRG	0.057	0.018	0.000		
RANGGYR	0.005	0.005	0.008	0.000	
ROTP	0.589	0.364	0.545	0.746	0.000
RLNTNUC	0.362	0.951	0.849	0.974	0.450
RCAUDNUC	0.320	0.917	0.422	0.871	0.032
RTHAL	0.815	0.958	0.608	0.812	0.519

	RLNTNUC	RCAUDNUC	RTHAL
RLNTNUC	0.000		
RCAUDNUC	0.003	0.000	
RTHAL	0.904	0.209	0.000

PARTIAL CORRELATIONS

	LBROCA	RBROCA	LDF1	RDF1	LDF2
LBROCA	1.000				
RBROCA	0.426	1.000			
LDF1	0.643	0.606	1.000		
RDF1	0.610	0.784	0.795	1.000	
LDF2	0.453	0.653	0.803	0.805	1.000
RDF2	0.344	0.592	0.789	0.899	0.825
LINFRONT	0.556	0.176	0.259	0.258	-0.180
RINFRONT	0.146	0.248	0.118	0.174	-0.236
LMOTOR	0.457	0.246	0.603	0.412	0.576
RMOTOR	0.438	0.570	0.745	0.732	0.867
LSENSORY	0.253	-0.167	0.502	0.188	0.345
RSENSORY	-0.179	0.193	0.229	0.422	0.270

	RDF2	LINFRONT	RINFRONT	LMOTOR	RMOTOR
RDF2	1.000				
LINFRONT	0.039	1.000			
RINFRONT	0.057	0.847	1.000		
LMOTOR	0.503	-0.055	-0.175	1.000	
RMOTOR	0.778	-0.234	-0.298	0.791	1.000
LSENSORY	0.360	0.005	-0.137	0.726	0.532
RSENSORY	0.555	-0.151	-0.057	0.182	0.422

	LSENSORY	RSENSORY
LSENSORY	1.000	
RSENSORY	0.333	1.000

MATRIX OF PROBABILITIES

	LBROCA	RBROCA	LDF1	RDF1	LDF2
LBROCA	0.000				
RBROCA	0.167	0.000			
LDF1	0.024	0.037	0.000		
RDF1	0.035	0.003	0.002	0.000	
LDF2	0.140	0.021	0.002	0.002	0.000
RDF2	0.273	0.042	0.002	0.000	0.001
LINFRONT	0.060	0.584	0.416	0.418	0.577
RINFRONT	0.650	0.436	0.715	0.588	0.460
LMOTOR	0.135	0.440	0.038	0.183	0.050
RMOTOR	0.155	0.053	0.005	0.007	0.000
LSENSORY	0.428	0.603	0.096	0.558	0.273
RSENSORY	0.577	0.549	0.473	0.172	0.395

MATRIX OF PROBABILITIES

	RDF2	LINFRONT	RINFRONT	LMOTOR	RMOTOR
RDF2	0.000				
LINFRONT	0.903	0.000			
RINFRONT	0.860	0.001	0.000		
LMOTOR	0.096	0.866	0.587	0.000	
RMOTOR	0.465	0.346	0.002	0.000	0.000
LSENSORY	0.251	0.989	0.671	0.007	0.075
RSENSORY	0.062	0.640	0.861	0.572	0.173

	LSENSORY	RSENSORY
LSENSORY	0.000	
RSENSORY	0.290	0.000

PARTIAL CORRELATIONS

	LWERNICK	RWERNICK	LSPRMRG	RSPRMRG	LANGGYR
LWERNICK	1.000				
RWERNICK	0.509	1.000			
LSPRMRG	0.271	-0.056	1.000		
RSPRMRG	0.265	0.665	0.275	1.000	
LANGGYR	0.576	0.469	0.432	0.519	1.000
RANGGYR	0.324	0.747	-0.173	0.721	0.603
LOTP	0.418	0.112	-0.403	-0.026	-0.238
ROTP	0.543	0.288	-0.256	-0.195	0.035

	RANGGYR	LOTP	ROTP
RANGGYR	1.000		
LOTP	0.169	1.000	
ROTP	0.105	0.495	1.000

MATRIX OF PROBABILITIES

	LWERNICK	RWERNICK	LSPRMRG	RSPRMRG	LANGGYR
LWERNICK	0.000				
RWERNICK	0.091	0.000			
LSPRMRG	0.394	0.862	0.000		
RSPRMRG	0.406	0.018	0.387	0.000	
LANGGYR	0.050	0.124	0.160	0.084	0.000
RANGGYR	0.305	0.005	0.593	0.008	0.038
LOTP	0.176	0.730	0.194	0.936	0.457
ROTP	0.068	0.364	0.422	0.545	0.914

	RANGGYR	LOTP	ROTP
RANGGYR	0.000		
LOTP	0.599	0.000	
ROTP	0.746	0.102	0.000

PARTIAL CORRELATIONS

	LLNTNUC	RLNTNUC	LCAUDNUC	RCAUDNUC	LTHAL
LLNTNUC	1.000				
RLNTNUC	0.746	1.000			
LCAUDNUC	0.848	0.642	1.000		
RCAUDNUC	0.855	0.769	0.725	1.000	
LTHAL	0.508	0.048	0.327	0.564	1.000
RTHAL	0.371	0.039	0.110	0.391	0.823

MATRIX OF PROBABILITIES

	LLNTNUC	RLNTNUC	LCAUDNUC	RCAUDNUC	LTHAL
LLNTNUC	0.000				
RLNTNUC	0.005	0.000			
LCAUDNUC	0.000	0.024	0.000		
RCAUDNUC	0.000	0.003	0.008	0.000	
LTHAL	0.092	0.883	0.299	0.056	0.000
RTHAL	0.235	0.904	0.734	0.209	0.001

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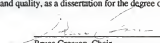Raichle, M. E. (1983). Positron emission tomography. Annual Review of Neuroscience, 6, 249-267.

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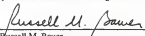
BIOGRAPHICAL SKETCH

David James Graves Williamson, son of James and Barbara Williamson, was born in Bridgeport, Connecticut, on May 6, 1966. He was raised in Lynchburg, Virginia, and earned his high school diploma from Heritage High School in 1984 with honors in English. Mr. Williamson conducted his undergraduate studies at Duke University, graduating cum laude with a Bachelor of Arts degree in psychology in May, 1987. During his junior and senior years, he served as president of the Duke University chapter of Psi Chi, the national psychology honorary society. In August 1987, he entered the doctoral graduate program in clinical and health psychology at the University of Florida and was granted a traineeship by the National Institute of Dental Research. Mr. Williamson received his Master of Science degree in August, 1990. While a student at the University of Florida, he received the Molly Harrower Award for Excellence in Psychodiagnostic Assessment and the Robert Levitt Award for Excellence in Neuropsychological Research. Mr. Williamson is currently living with his wife and two dogs while pursuing post-doctoral training in neuropsychology at the University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma.
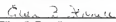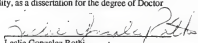
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Bruce Crosson, Chair
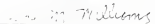Associate Professor of Clinical and Health Psychology

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Russell M. Bauer
Associate Professor of Clinical and Health Psychology

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Eileen B. Fennell
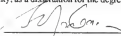Professor of Clinical and Health Psychology

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Kenneth M. Heilman
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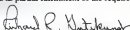
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This dissertation was submitted to the Graduate Faculty of the College of Health Related Professions and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 1992

Dean, College of Health Related Professions

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